I. Model studies on the formation of the dibenzofuranoquinone core of popolohuanone E. II. Diene precursors for decalin synthesis.

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I. Model Studies on the Formation of the Dibenzofuranoquinone Core of Popolohuanone E.

II. Diene Precursors for Decalin Synthesis.

by

Bonnie L. Martinez

Presented to the Graduate and Research Committee
Of Lehigh University
In Candidacy for the Degree of
Doctor of Philosophy
in
The Department of Chemistry

Lehigh University
October 2001

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10/19/01
Date

John W. Benbow, Ph. D., Dissertation Director

12/07/07
Accepted Date

Committee Members

Natalie Foster, Ph. D. Committee Chair

John Larsen, Ph. D.

William Kinney, Ph.D.

In memory of my mother,
Barbaranne Theresa Farr Anstatt (1940-1998).

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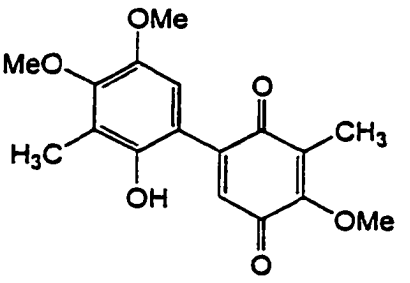
Abstract

Popolohuanone E, isolated from the Pohnpei marine sponge *Dysidea* sp., exhibits selective cytotoxicity towards human non-small cell lung cancer cells due to potent topoisomerase-II inhibitor activity. It possesses an unusual perhydroxylated benzofuranoquinone core that is believed to have been formed via an oxidative dimerization of *cis*-fused decalin substituted arenols. Our research focus has been twofold: i) utilize the molecular symmetry to devise an oxidative dimerization pathway to the unusual aromatic system and ii) employ the intramolecular Diels-Alder (IMDA) reaction to synthesize the decalin fragments in a stereocontrolled fashion.

The hydroxyquinone precursor, **A**, for the formation of the dibenzofuran-1,4-dione core was prepared using a Suzuki protocol for biaryl systems. The conditions for the formation of the sensitive aryl anions, the choice of borating agent and the selection of protecting groups for this protocol are discussed.



A

The acid catalyzed cyclization of hydroxyquinone **A** provided several dimeric quinone products that were derived from complex electron transfer processes. Possible

mechanisms for the formation of these dimeric products are discussed. Modifications of the protocol that led to new monomeric dibenzofurans were examined and several examples utilizing the process are provided.

To investigate an IMDA cyclization approach to popolohuanone E, a synthesis of dienes with the stereochemical features required for the decalin core, including the *syn*-dimethyl arrangement, needed to be developed. The oxidation of silyl enol ethers derived from the stereocontrolled addition of copper reagents to substituted cyclopentenones gave respectable yields of the desired α-hydroxy ketones. Cleavage of these systems with lead tetraacetate and homologation with Yamamoto's allyl phosphine oxide reagent provided an efficient synthesis of the stereochemically-defined dienes. These systems could prove to be useful partners for an IMDA approach to the decalin core of clerodane systems.

Chapter 1

Model Studies on the Formation of the Dibenzofuranoquinone Core of Popolohuanone E

Introduction

Natural products are an important source of new drugs for clinical use, especially in the treatment of diseases such as cancer. Currently in the United States, cancer is the second leading cause of death and is projected to become the leading cause within a few years.[1] Studies have also shown that the overall cancer death rate would be declining except for the annual increase in the lung cancer death rate.[2] World wide, the increasing incidence of lung cancer is largely due to accumulated active and passive exposure to tobacco products.[3] Other causes of lung cancer include exposure to asbestos, irradiation of uranium miners, chromate and nickel as industrial hazards and automobile exhaust. To date, the existing strategies for lung tumor treatments are not effective and, consequently, a greater emphasis is being placed on prevention due to the lack of cures.

In a healthy body, the respiratory epithelium in our respiratory tracts has evolved to clean, moisten and warm inhaled air and to lubricate and sweep particulate matter and fluid from the smaller to larger airways where foreign material is expelled by coughing.[4] Any interference with normal ciliary movement or secretion of mucus disturbs the normal housecleaning mechanism of the lungs and changes the respiratory epithelium into squamous epithelium which have no cilia. In turn, the loss of cilia prevents the ability to expel mucous laden with dust and bacteria and exposes the bronchi to hot dry gases, particulates and carcinogens. Eventually, the accumulation of this matter in the lungs leads to an infection such as bronchitis or broncho-pneumonia. Traditional treatment with antibiotics can cure a bronchial infection, but with cancer, infection-like symptoms immediately reoccur and cannot be alleviated by traditional methods. Repeated exposure

can lead to the formation of squamous cell carcinoma of the bronchus, a consequence that ultimately leads to lung cancer.

Lung tumors have been classified into two categories based on their characteristics.[3] Small cell lung cancer (SCLC) makes up 25% of all lung cancers and has very distinct characteristics making it easy to diagnose. Even though this aggressive tumor disseminates very early, it is very responsive to chemotherapy. All other types of lung cancers are classified as non-small cell lung cancers (NSCLC) and are a collection of several histologically distinct forms such as squamous cell carcinomas, adenocarcinomas, bronchiolalveolar carcinomas, large cell carcinomas and undifferentiated carcinomas. NSCLC has a predisposition to local invasion in the chest and is difficult to cure due to reduced responsiveness to standard chemotherapy or radiation treatments. Hence, surgical resection is the primary treatment modality, but still may not lead to an ultimate cure. The success of curing the cancer by surgery is largely dependent upon finding the cancer at an early stage, otherwise a late diagnosis may show that the cancer has already metastasized.[4] At this point, surgical treatments become less curative and the use of chemotherapeutic agents is necessary. To date, only a handful of cytotoxic agents have yielded lasting remissions and, in most cases, their use is largely only palliative for the advanced diseased state.

The DNA topoisomerase enzymes play an important role in the cytotoxic action of drugs due to their involvement in DNA replication.[5] The topoisomerases often are targeted by chemotherapeutics because cancerous cells replicate more quickly than surrounding healthy cells. By inhibiting these enzymes, hopefully, replication of rapidly proliferating cancerous cells will cease.

Practically all DNA *in vivo* is supercoiled and must be untwisted and unwound to replicate. The topoisomerase enzymes are involved in the unwinding of the DNA double helix and the separation of newly replicated DNA.[6] Initially, they form a complex with the DNA and then roll along the DNA to release the supercoiling. At any one time, a portion of the DNA complex is supercoiled while another portion is uncoiled (Figure 1).[7]

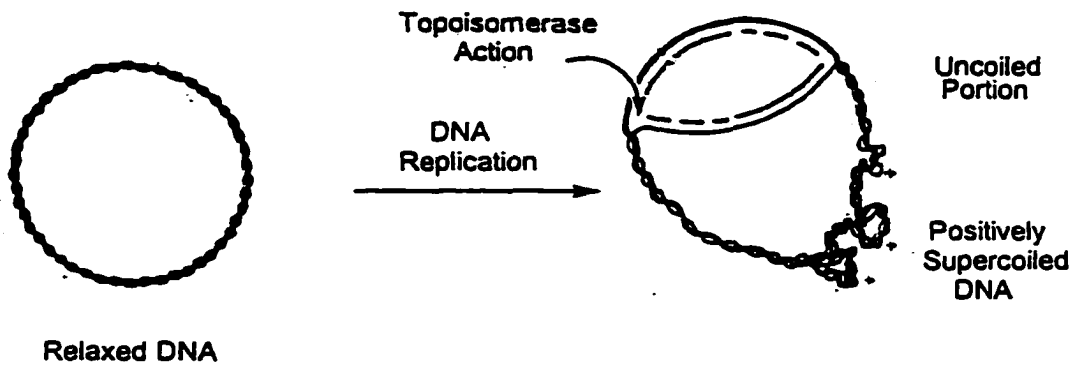


Figure 1

There are two types of topoisomerases, type I and type II (top1 and top2), that can either induce or remove knots or links in a chain of DNA.[7] Both top1 and top2 catalyze the unlinking of the DNA strands by making transient DNA strand breaks which allow the DNA to rotate around or traverse these breaks.[8] The top1 enzymes cut a single strand of the double helix (Figure 2) and allow the topologically constrained DNA to relax. Inhibitors of top1 (labeled as drug in Figure 2) prevent the resealing of top1-mediated DNA single stranded breaks by stabilizing and prolonging the DNA-Top1 complex. The enzyme undergoes a conformational change and becomes a cleavable complex (DNA + enzyme + drug) that may eventually succumb to degradation by other nucleases and halt the replication process.

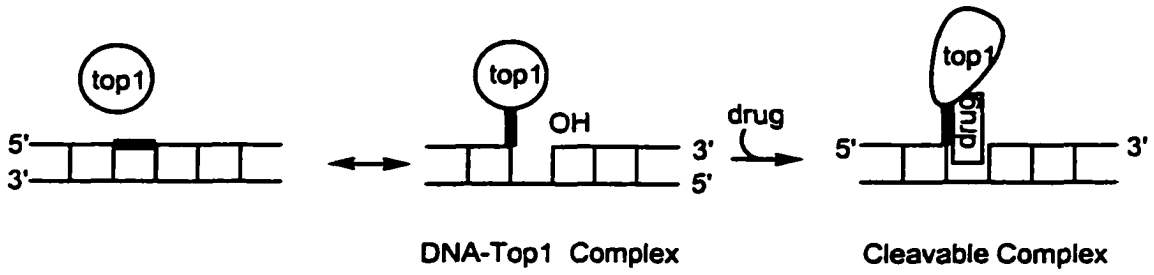


Figure 2

In the case of top2, the enzyme is linked to both DNA strands as a homodimer that cleaves both strands of the DNA (Figure 3). As with the top1 inhibitors, top2 inhibitors stabilize the cleavable complexes and prevent the relegation of the DNA strands. This halts the unwinding process required for replication and without which the cell dies.

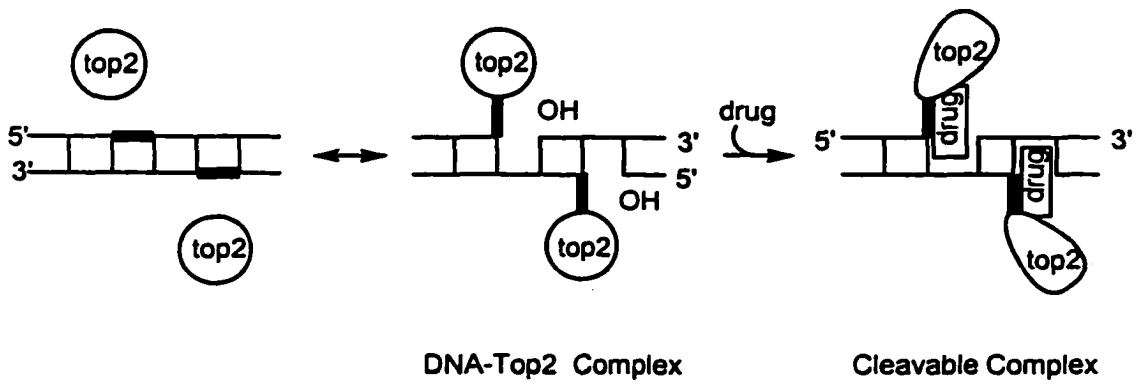
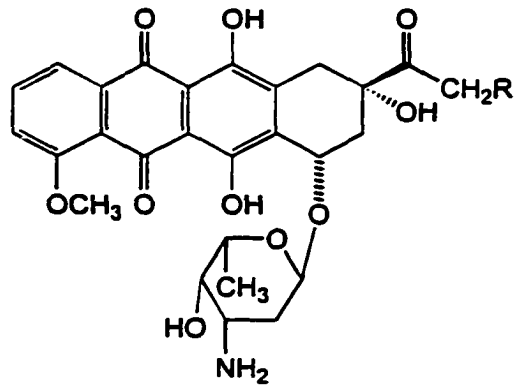


Figure 3

The anthracycline antibiotics are one of the most important classes of drugs used to treat lung cancer.[9] In the 1960's, two drugs in this class, doxorubicin 1 (adriamycin) and daunorubicin 2 (daunomycin) (Figure 4), were introduced that are now



1 R = OH Doxorubicin

2 R = H Daunorubicin

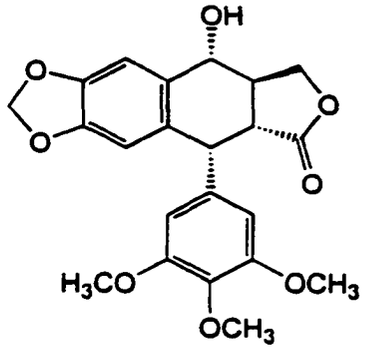
Figure 4

useful tools to probe the underlying chemical and biochemical processes of cancer progression. Convincing arguments have been made that implicate either DNA binding or the free radical generation as the mode of action of these drugs.[10] Both compounds are known to bind avidly to DNA by intercalation, which inhibits DNA replication and RNA transcription. Topoisomerase II has also been identified as a possible key target, but the mechanism by which its inhibition occurs is still unknown.

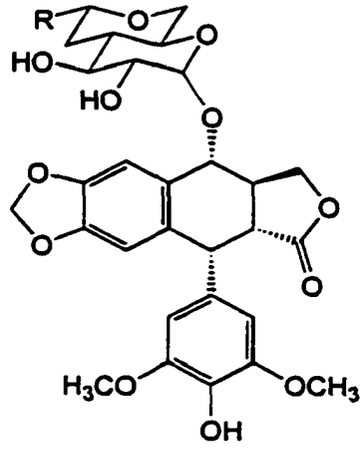
The use of 1 and 2 as chemotherapeutics has several disadvantages. In many cases, the tumors may initially respond to the anthracyclines, but over time they develop resistance that often extends to other chemically unrelated drugs.[11] The phenomena associated with this resistance includes: (a) reduced intracellular drug accumulation, (b) changes in drug metabolism, (c) alteration of intracellular targets, and (d) increased DNA repair potential.[12] Another major drawback is the chronic cardiotoxicity that imposes limitations on the dose level and on the number of drug courses.[11] This is especially important in younger patients where the effects have been found to be long lasting.[13] Chemo-therapeutics also suffer from a lack of specificity leading to the destruction of

rapidly growing normal cells (as in the bone marrow and in the gastrointestinal mucosa) along with cancerous cells. A delicate balance must be maintained so that the normal cells are given time to recuperate while the cancerous cells receive a cumulative toxic effect.

The podophyllotoxins are another important class of chemotherapeutics used to treat lung cancer; podophyllotoxin **3** is the aglycone of the derivatives etoposide **4** and teniposide **5** (Figure 5).[14] Podophyllotoxin has had very limited use as an anticancer agent due to its severe toxic side effects, but both **4** and **5** are currently in clinical use and have almost become the standard of therapy for both testicular cancer and small cell lung cancer via topoisomerase II inhibition.



3 Podophyllotoxin



4 R = CH_3, Etoposide

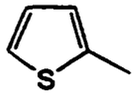
5 R =  , Teniposide

Figure 5

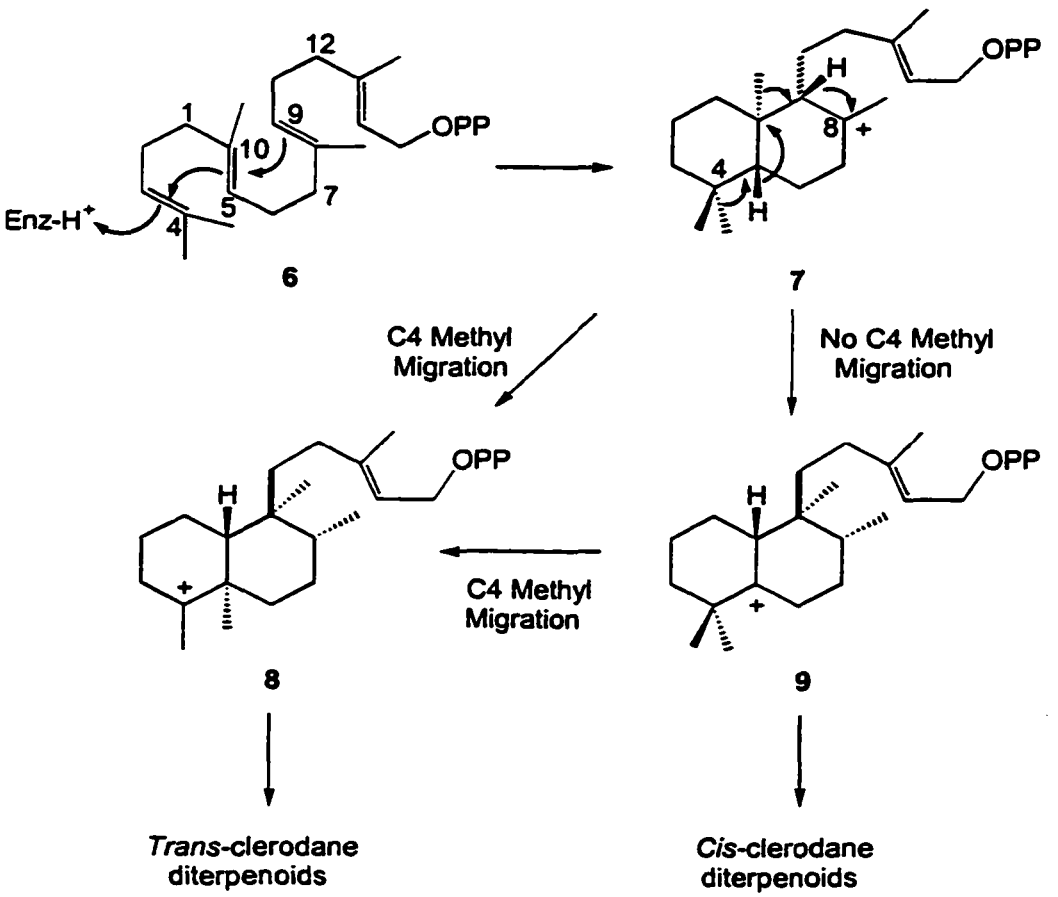
Etoposide, by itself, is most commonly used for the treatment of SCLC and is applied in combination therapy for the treatment of NSCLC. Interestingly, one study proposes that the reason SCLC is more responsive to both **4** and **5** is because the top2 content in nuclear protein appeared to be higher in SCLC cell lines than in NSCLC.[15] Each of these drugs has major drawbacks to its use including myelosuppression, neutropenia, nausea, alterations in normal respiratory functions and the development of tumor cell resistance.[16,17]

Clearly, new therapeutic options are needed that provide antitumor efficacy, reduced toxicities and reduced drug resistance caused by tumor instability. Natural products are and will continue to be an important source in the development of these novel therapeutic agents. However, because of the low availability of naturally occurring therapeutic substances, efficient access to synthetic analogues is required to provide an adequate supply for further testing.

Background

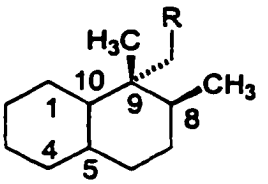
The diterpenoids are one biologically and medicinally important class of natural products composed of several subsets including the clerodanes. Via a series of methyl and hydride shifts, the clerodane family is believed to be related to the labdanes that are themselves derived from geranylgeranylpyrophosphate **6** (Scheme I).[18] Clerodane diterpenoids are classified into two major groups, *cis*- and *trans*-, with respect to the decalin ring configuration. Initially, acid catalyzed ring closure between C9 and C10 of geranyl-geranylpyrophosphate followed by ring closure between C5 and C4 provides a cation at

C8. By a series of methyl and hydride shifts, the *trans*-clerodanes can arise from intermediate **8**. The *cis*-clerodanes require intermediate **9** that may eventually lead to either the thermodynamically more stable *trans*-decalins or the less common *cis*-decalins depending on which of the C4 methyls migrate.



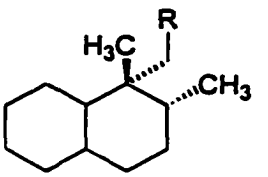
Scheme I

The proposed biosynthesis provides both *cis*- and *trans*-clerodanes that are characterized as having a decalin ring system containing four contiguous stereogenic centers at C5, C8, C9 and C10 (Figure 6). The vicinal *syn*- or *anti*-dimethyls at positions C8 and C9, with the C9 methyl existing at a quaternary center, pose an even greater



10

syn-8,9-dimethyl-9-alkyl substituted decalin



11

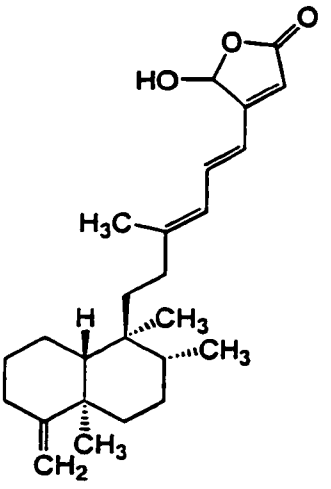
anti-8,9-dimethyl-9-alkyl substituted decalin

Figure 6

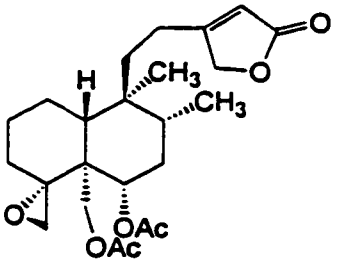
synthetic challenge due to an increased level of difficulty to install quaternary centers with a high degree of stereocontrol.

A broad spectrum of biological activity is associated with the clerodanes. Representative examples of *trans*-congeners include the antimicrobial (±)-palauolide **12**,[19] the insect antifeedant ajugarin I **13**,[20] and the multiply active anti-HIV, antimicrobial, antiinflammatory, antimitotic, and antisecretive ilimaquinone **14**[21] (Figure 7). Examples of biologically relevant *cis*-fused clerodanes are the antimicrobial ageline B **15**,[22] the piscicidal agent solidagolactone VIII **16**,[23] and the topoisomerase-II inhibitor popolohuanone E **17**.[24]

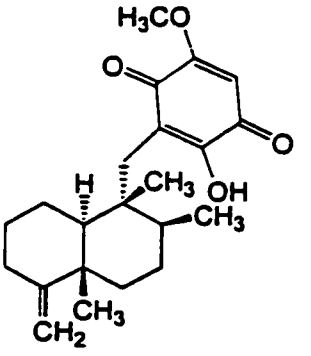
The isolation of popolohuanone E from the *Dysidea* sponge as a dark purple solid was reported in 1993.[24] The unusual cytotoxicity **17** displays towards NSCLC and the inhibition of top2 at a relatively low concentration (IC_{50} = 400 nM)[24] make the compound an attractive target for organic synthesis. The inhibitory concentrations of **17** in both the top2 and the NSCLC bioassays are comparable to the inhibitory concentrations for the epipodophyllotoxins[25] and other anticancer agents currently in use, which suggests its possible use as a chemotherapeutic agent.



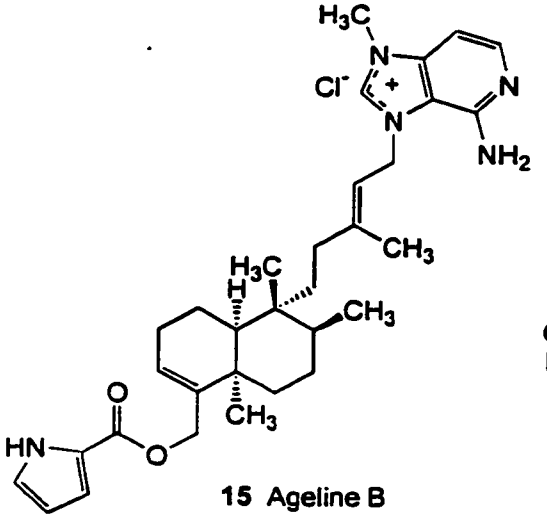
12 (±)-Palauolide



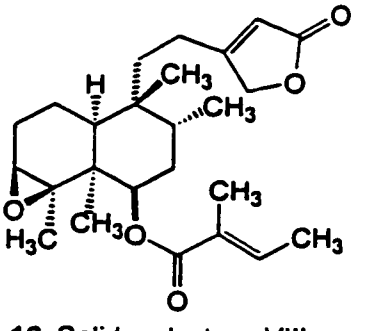
13 Ajugarin I



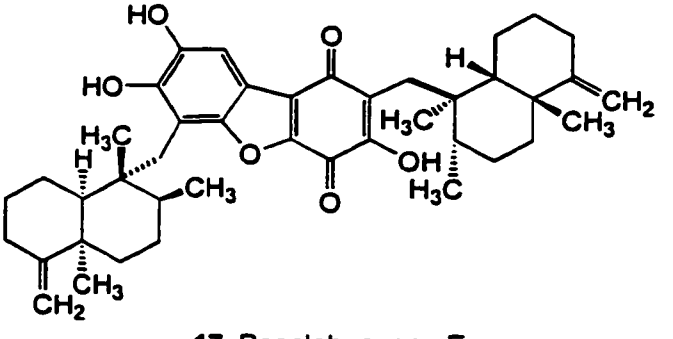
14 Ilimaquinone



15 Ageline B



16 Solidagolactone VIII



17 Popolohuanone E

Figure 7

The structural features of popolohuanone E include a highly oxygenated dibenzofuran-1,4-dione as the central core of the molecule that has not been observed elsewhere. Attached to the aromatic core are two identical and highly functionalized *cis*-fused decalin rings that contain quarternary centers. Scheuer suggests that **17** may have been formed by the oxidative dimerization of compounds like the as yet unreported 6'-hydroxyarenarol **18**; it is notable that a similar molecule, arenarol **19**, was also isolated from the sponge (Figure 8).[24] Ideally, the synthesis of popolohuanone E would take advantage of the symmetry of the molecule and use monomers similar to **18** in the construction of the overall product.

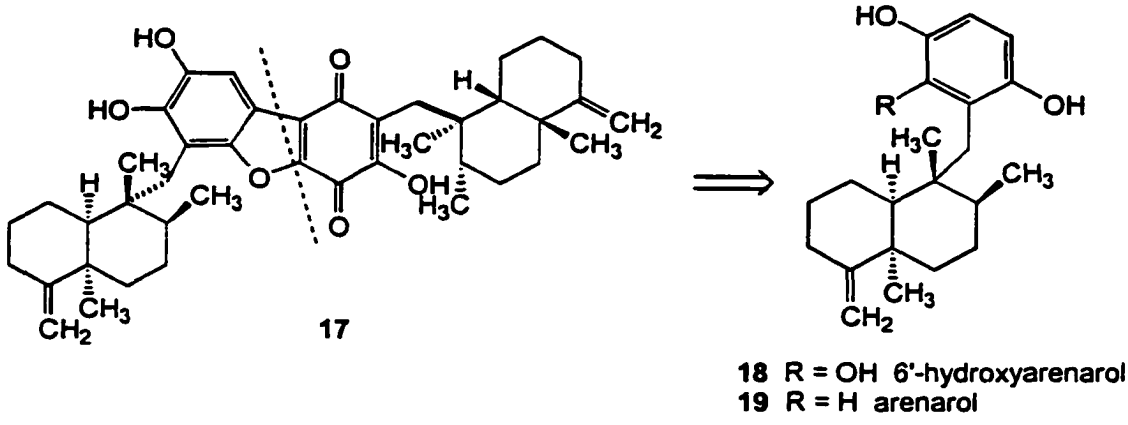
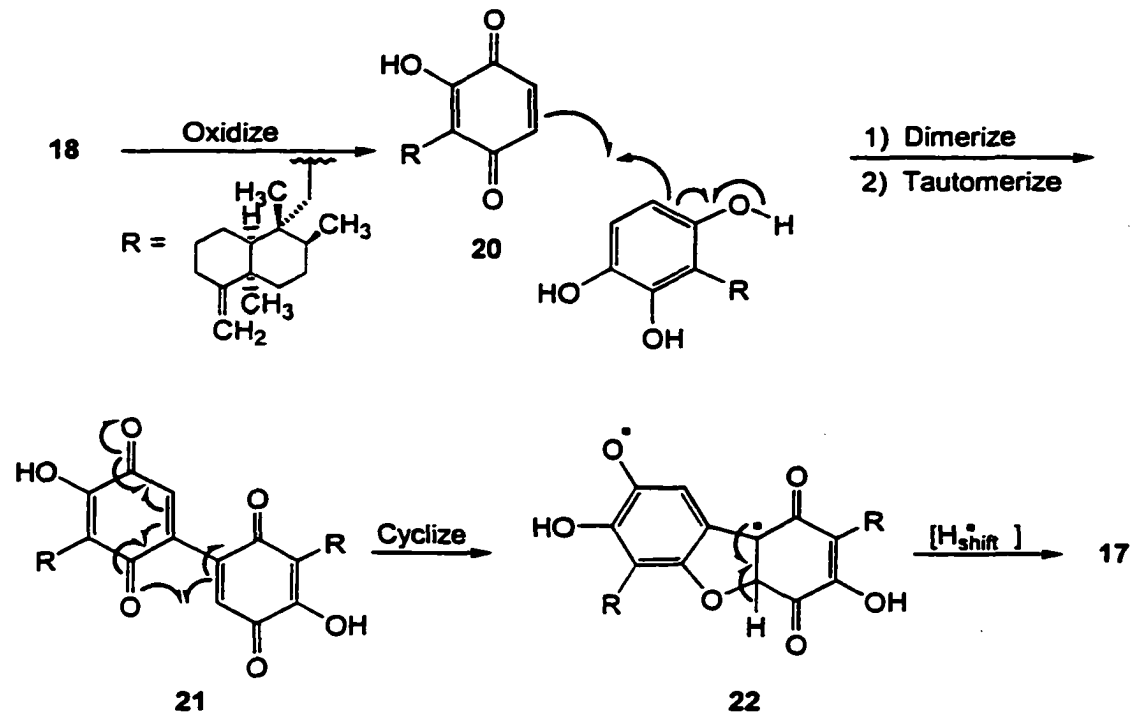


Figure 8

A possible biosynthetic step in the pathway leading to popolohuanone E from 6'-hydroxy-arenarol **18** may be oxidation by oxygen to provide the quinone **20** (Scheme II). Prolonged exposure to light or some other single electron transfer (SET) reagent could produce radicals that could dimerize and tautomerize to form the biaryl **21**. Subsequent cyclization would form the central furan ring of **22**, and a hydrogen atom extraction would provide the natural product **17**.



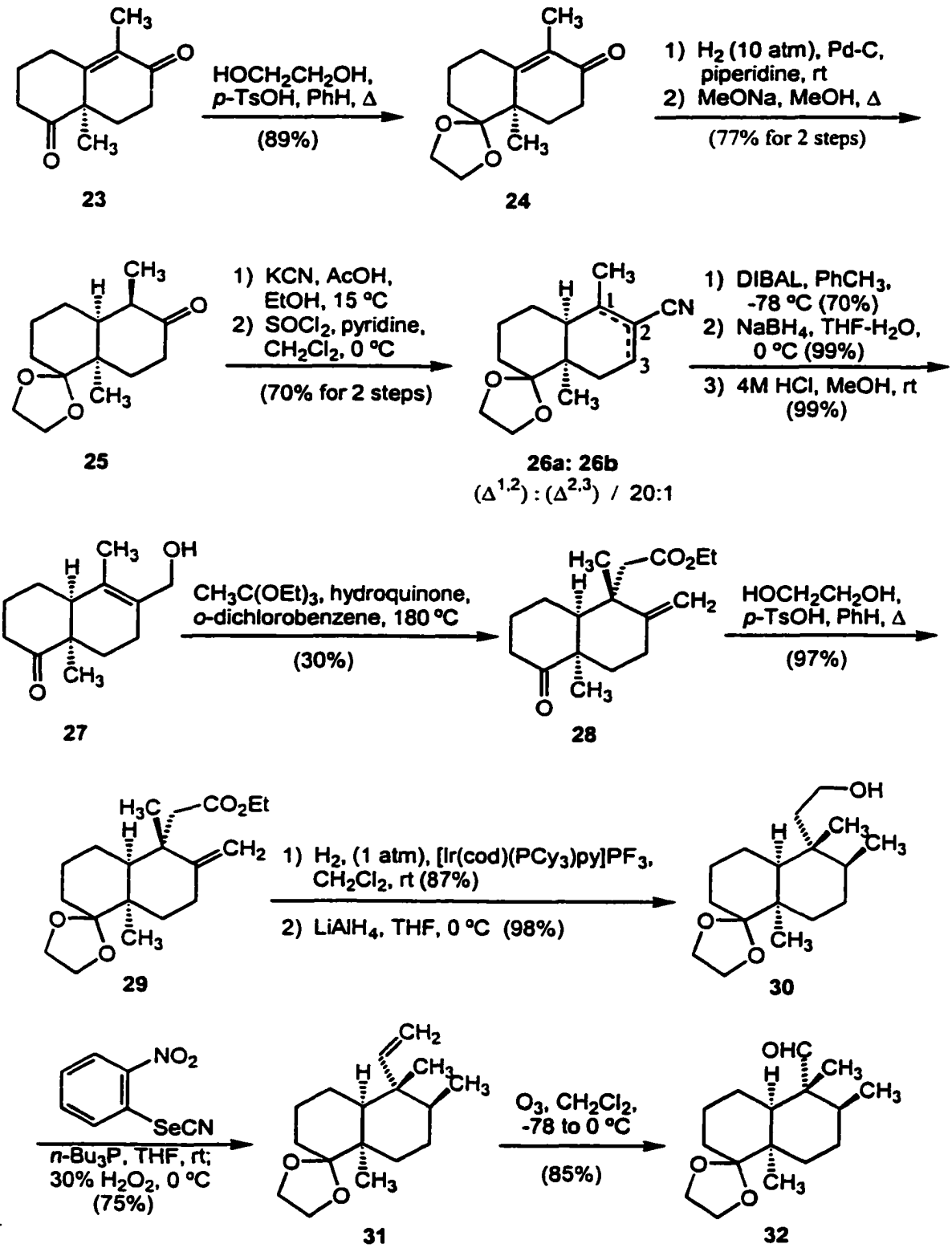
Scheme II

Arenol Synthesis

Terashima *et al.* recently reported on the overall synthesis of optically active popolohuanone E trimethyl ether.[26-30] Their synthesis features a highly regioselective annulation of a phenol with a dichloroquinone to prepare the aromatic core and uses the Wieland Miescher ketone to synthesize the *cis*-fused decalin segment. Beginning with the decalin, enantiomerically pure (-)-Wieland Miescher diketone **23** was selectively protected and the resulting ketal **24** was subjected to a stereocontrolled hydrogenation that provided the desired *cis*-fused decalin as a mixture of epimers that was epimerized to the more stable isomer **25** (Scheme III). Cyanohydrin formation followed by dehydration

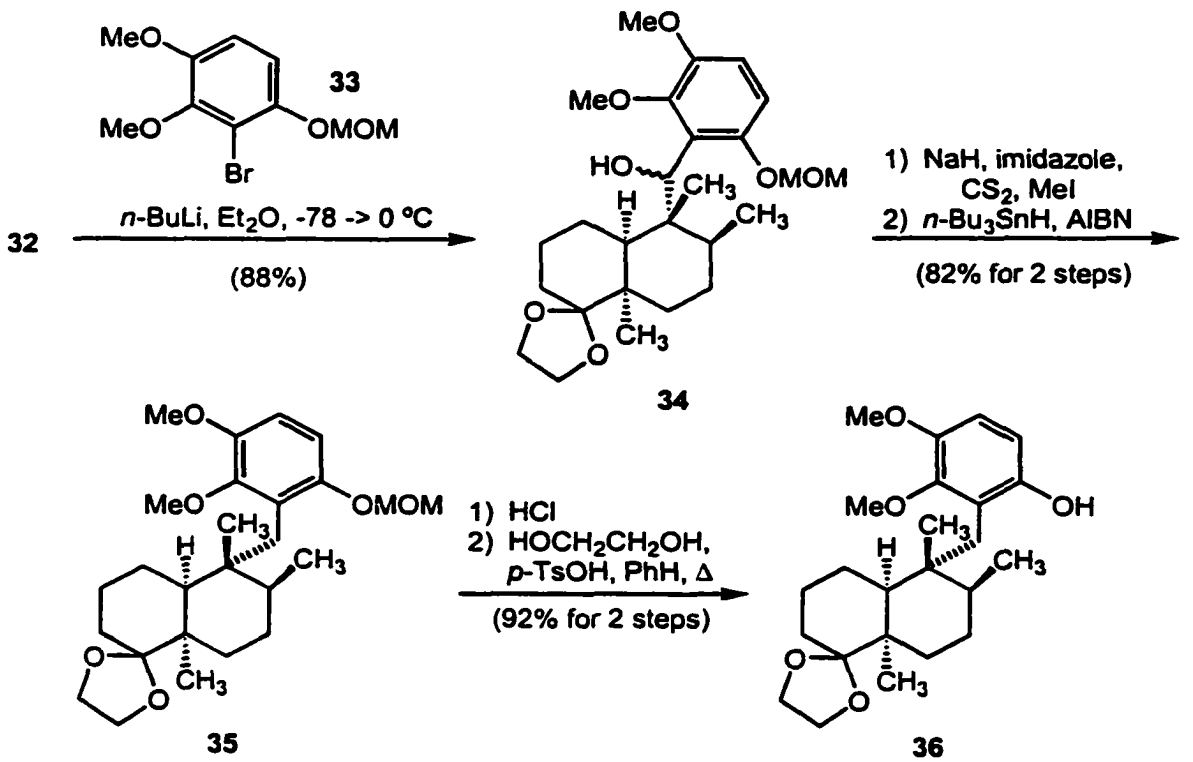
with thionyl chloride in pyridine yielded the nitriles **26a** and **26b**. This mixture was partially reduced using diisobutylaluminum hydride (DIBAL-H) to furnish a mixture of aldehydes that could be separated by recrystallization yielding the desired aldehyde as the major product. Subsequent reduction of the aldehyde with sodium borohydride ($NaBH_4$) and deprotection under acidic conditions gave the alcohol **27**.

The orthoester Claisen rearrangement was performed on **27** to provide a mixture of stereoisomers that were separable by column chromatography, affording ester **28** as the major product. Re-ketalization provided **29** that underwent a stereocontrolled reduction of the exocyclic olefin using the homogeneous catalyst $[Ir(cod)(PCy_3)py]PF_6$. Lithium aluminum hydride reduction of the ester then provided the alcohol **30** as a single stereoisomer. Conversion to the olefin **31** utilizing the two-step selenation/elimination followed by ozonolysis of the double bond gave the aldehyde **32** that would be used to prepare both the phenolic and the quinoidal portion of popolohuanone E trimethyl ether.



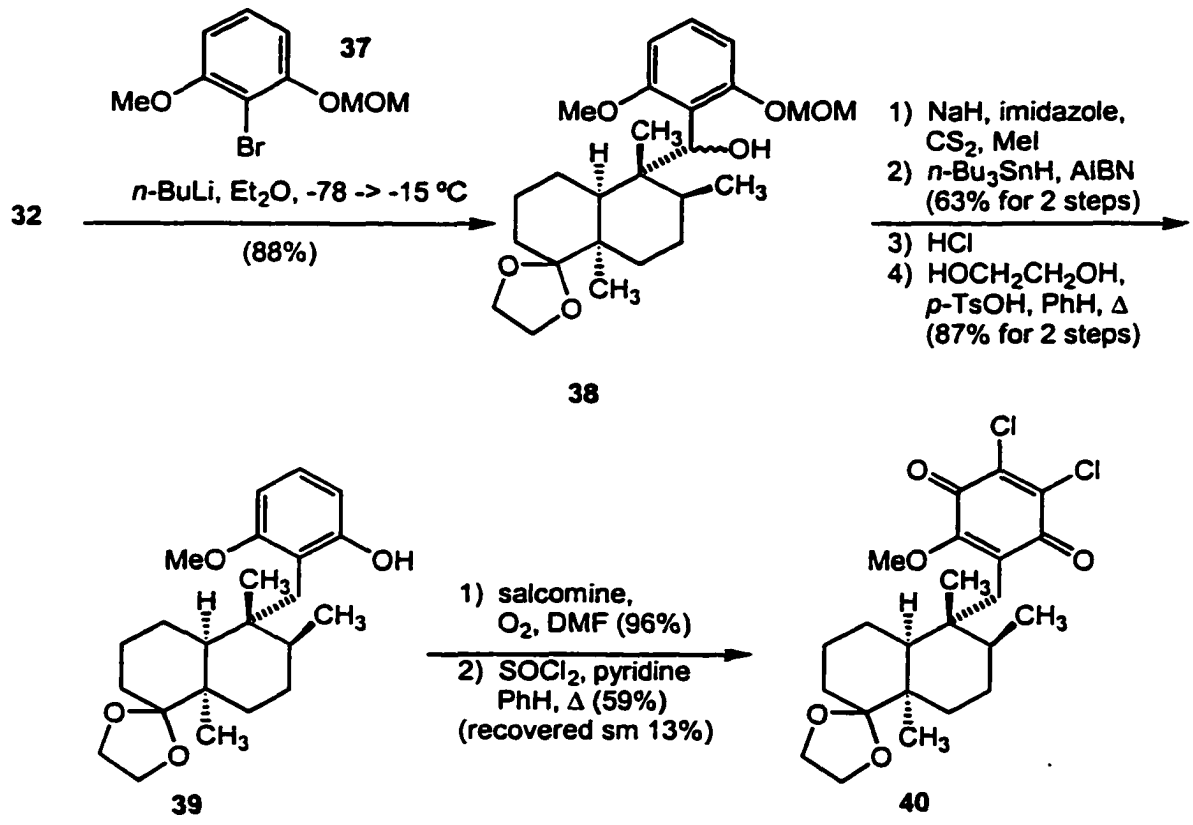
Scheme III

Addition of the aryl lithium generated from aryl bromide **33** to the aldehyde **32** furnished the alcohol **34** (Scheme IV). Barton deoxygenation provided the intermediate **35** which underwent the selective acidic removal of the methoxymethyl (MOM) protecting group in the presence of the arylmethoxy groups when subjected to acid. These conditions also exposed the ketone, which had to be reprotected to provide phenol **36**.



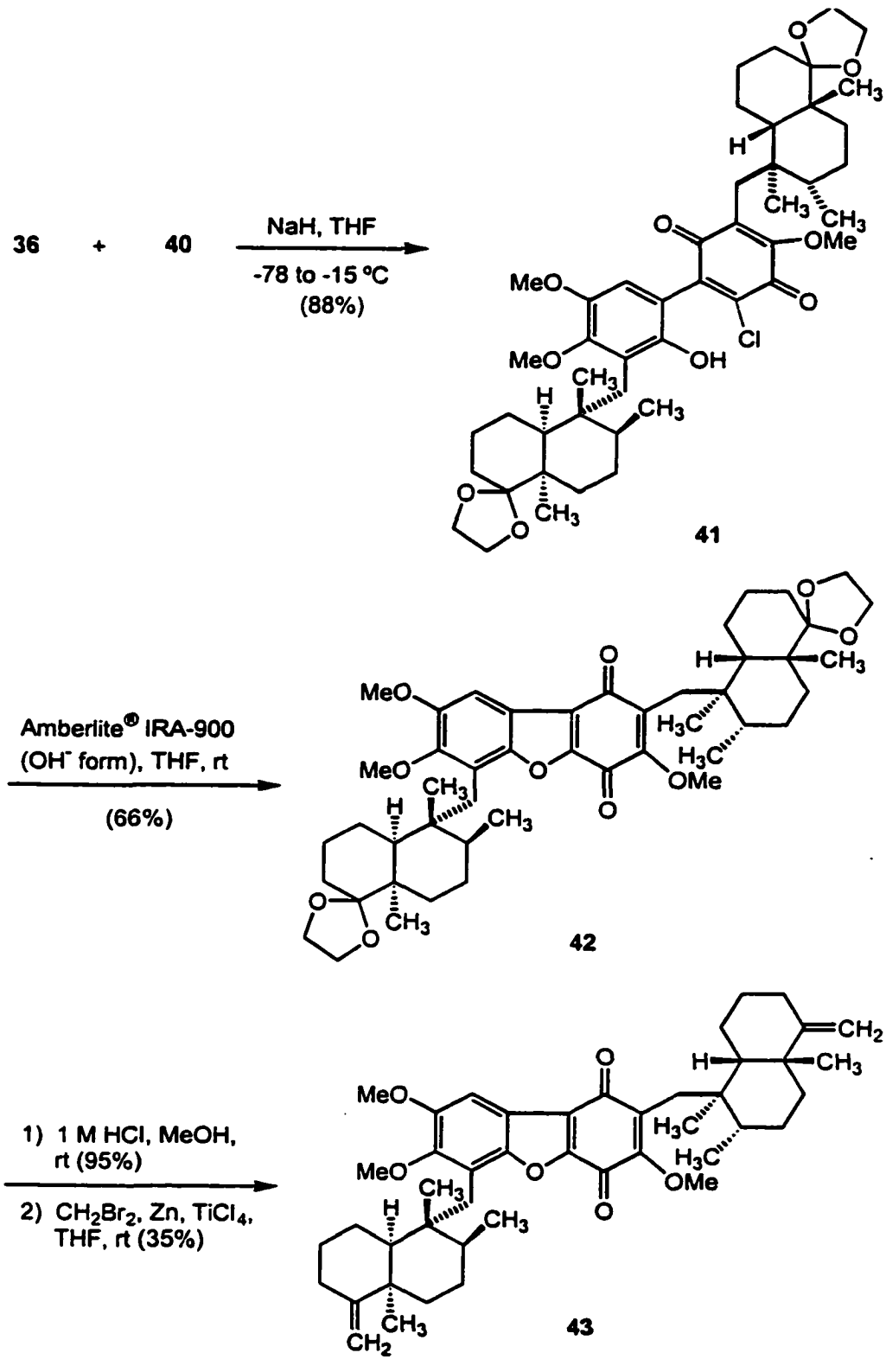
Scheme IV

The quinone was synthesized by addition of the aryl lithium generated from bromide **37** to aldehyde **32** to provide the benzylic alcohol intermediate **38** (Scheme V). Transformation via methodology similar to that described above provided the phenol **39**, which was oxidized to the quinone using salcomine and O_2 followed by treatment with thionyl chloride to afford the dichloroquinone **40**.



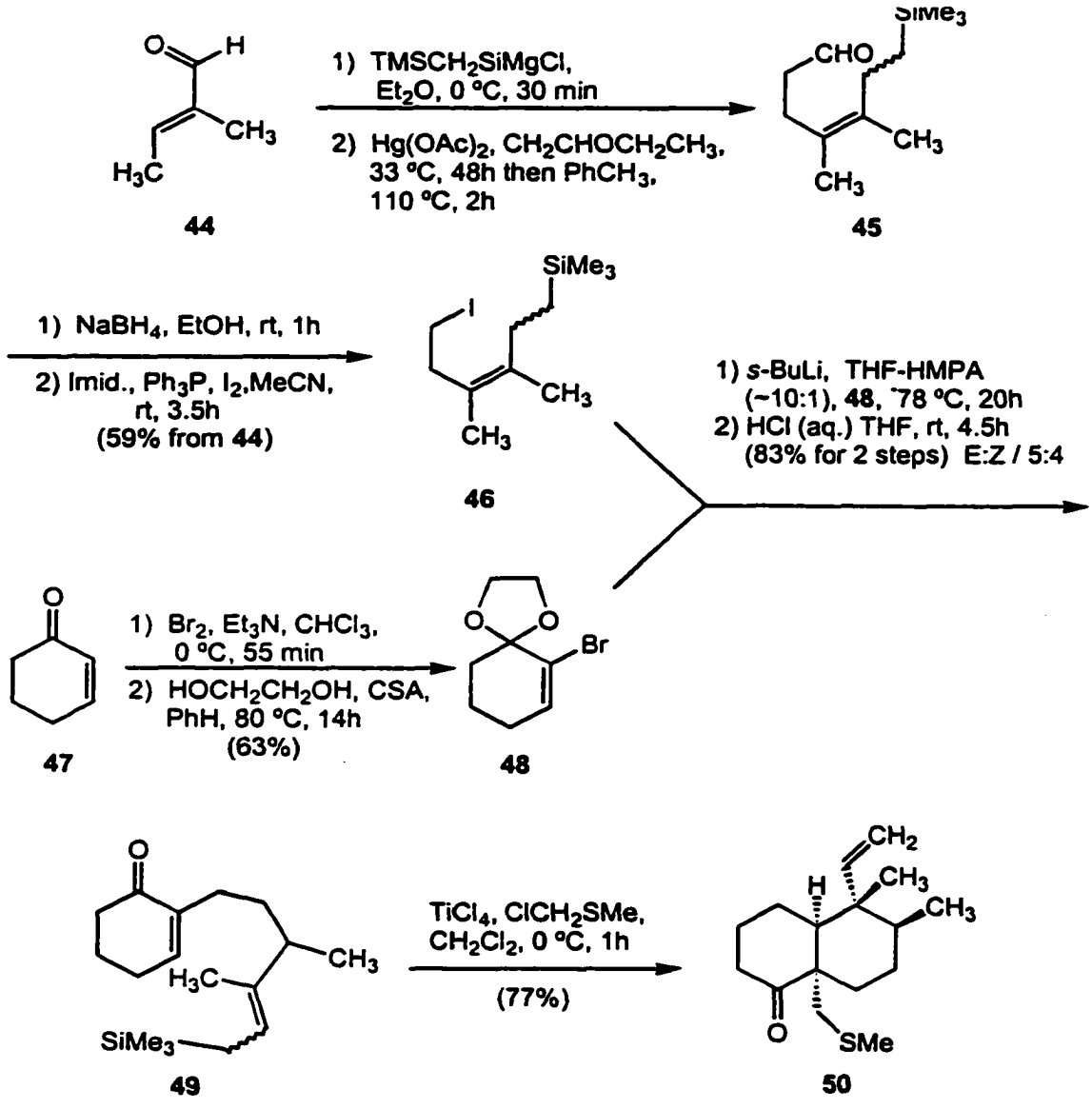
Scheme V

The key reaction for Terashima's total synthesis of popolohuanone E trimethyl ether was the regioselective ring formation reaction between **36** and **40**. In the presence of sodium hydride in THF at ⁻78 °C, the addition of quinone **40** to the phenoxide ion of **36** provided the C-substituted product **41** as a single regioisomer in high yield (88%) (Scheme VI). Subsequent ring closure was performed by exposure to Amberlite IRA-900 (OH^- form) in chloroform at 0 °C leading to the dibenzofuranoquinone **42**. Simultaneous deprotection of both ketals under acidic conditions with homologation to the exocyclic methylenes gave **43**, the trimethyl ether of popolohuanone E.



Scheme VI

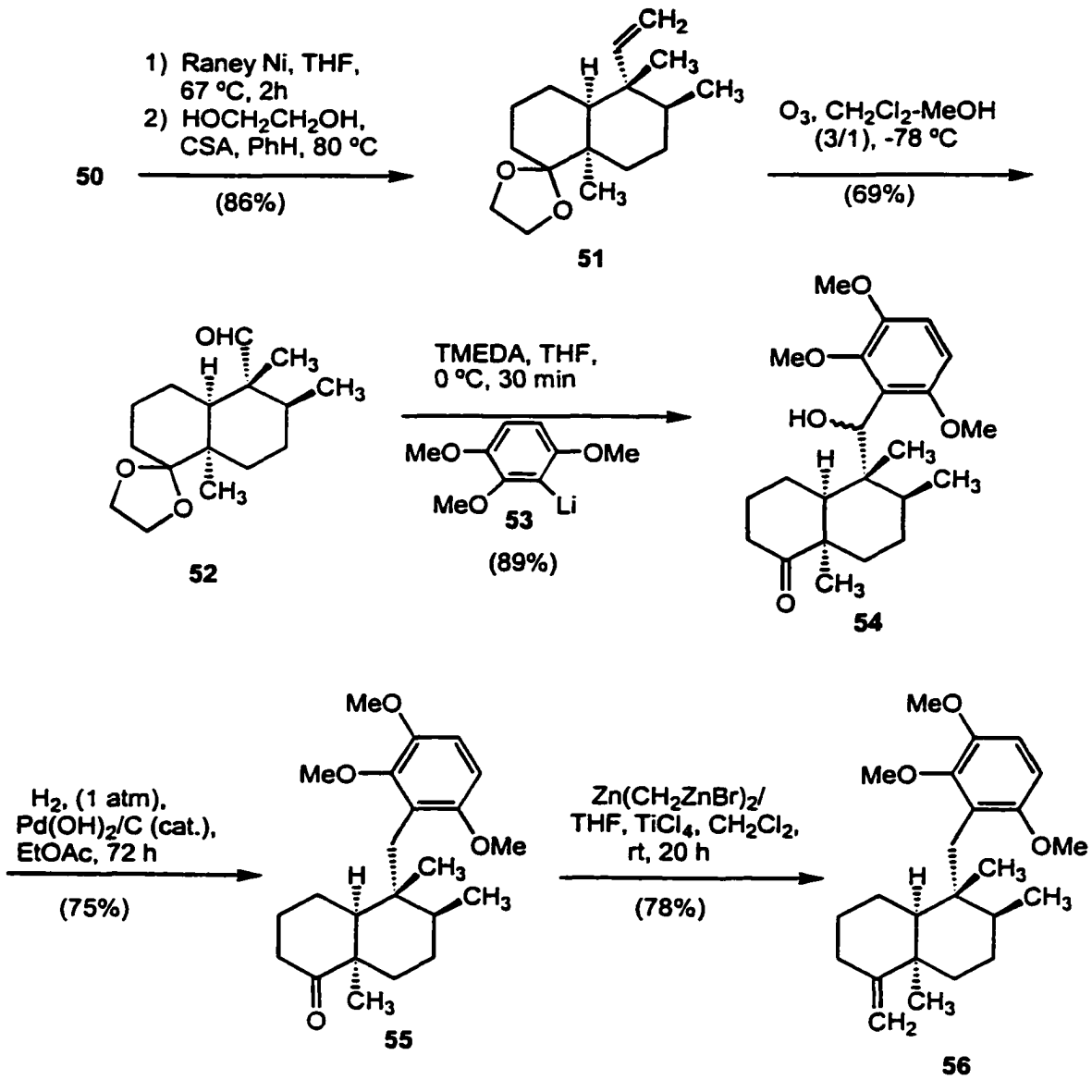
Although no reports on the overall synthesis of popolohuanone E **17** have appeared, two other groups have reported on the synthesis of arenarol **19**. Anderson and Pearson's[31] synthesis of **19** is a modification of the procedure of Tokoroyama[32] to prepare the *cis*-fused decalin (Scheme VII). To the aldehyde **44** was added the Grignard reagent Me_3SiCH_2MgCl that provided an allylic alcohol that was heated under Claisen rearrangement conditions affording the aldehyde **45**. The aldehyde was converted



Scheme VII

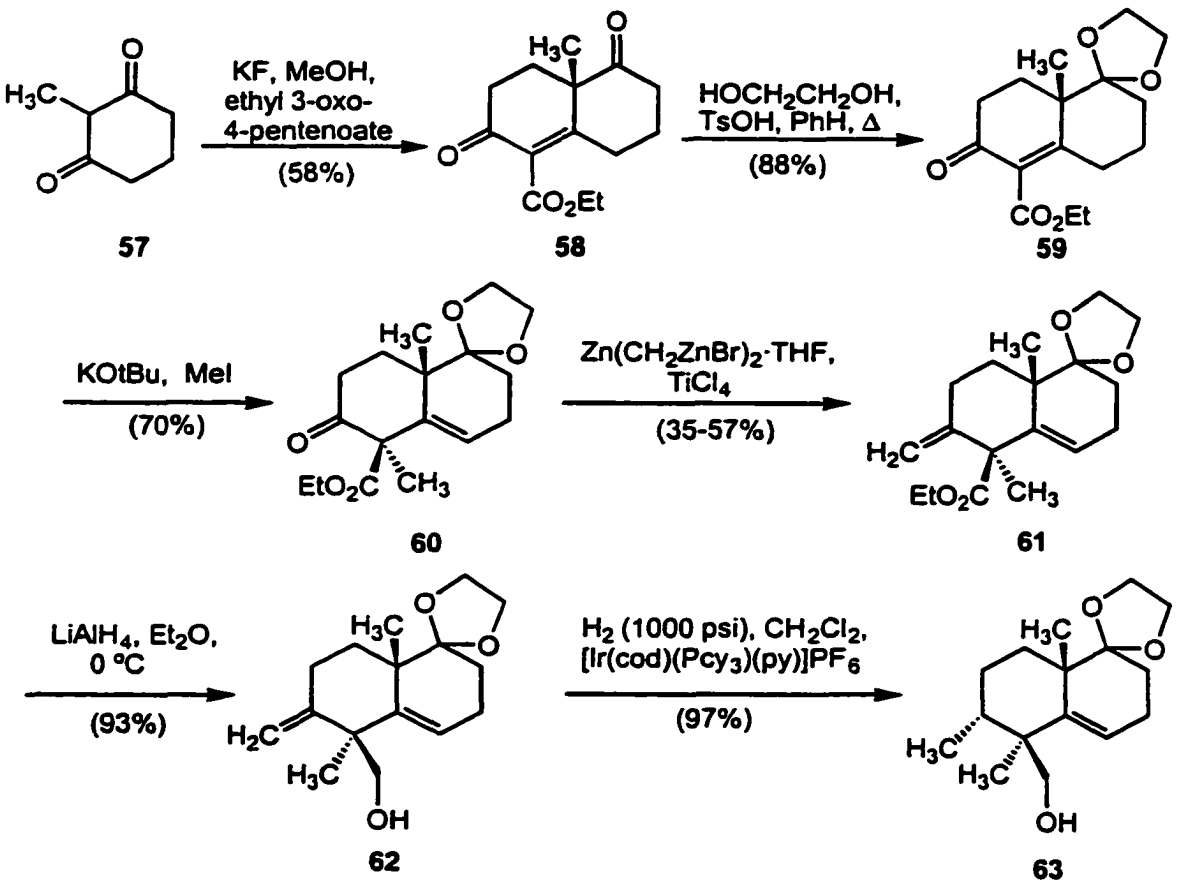
into the iodide **46** using standard methods (I_2, PPh_3). Cyclohexenone **47** was brominated and then protected to give the bromoketal **48**. To the lithium ion generated from **48** was added iodide **46**. Deprotection of the ketal using aqueous HCl gave **49** as a mixture of *E/Z* isomers that were subjected to an intramolecular Hosomi-Sakurai cyclization, mediated by titanium tetrachloride, with *in situ* trapping of the resultant enolate with $ClCH_2SMe$ to provide the *cis*-decalin **50**.

Desulfurization of **50** with Raney nickel followed by protection of the ketone afforded ketal **51** that was subjected to ozonloysis of the terminal alkene (O_3, PPh_3) to provide the aldehyde **52** (Scheme VIII). Addition of 2,3,6-trimethoxyphenyllithium **53** to the aldehyde **52** provided the benzylic alcohol **54** that underwent hydrogenolysis to afford a ketone **55** that was in turn reacted with Nysted's reagent to install the exocyclic methylene to provide 6'-hydroxy-(±)-arenarol trimethyl ether **56**.



Scheme VIII

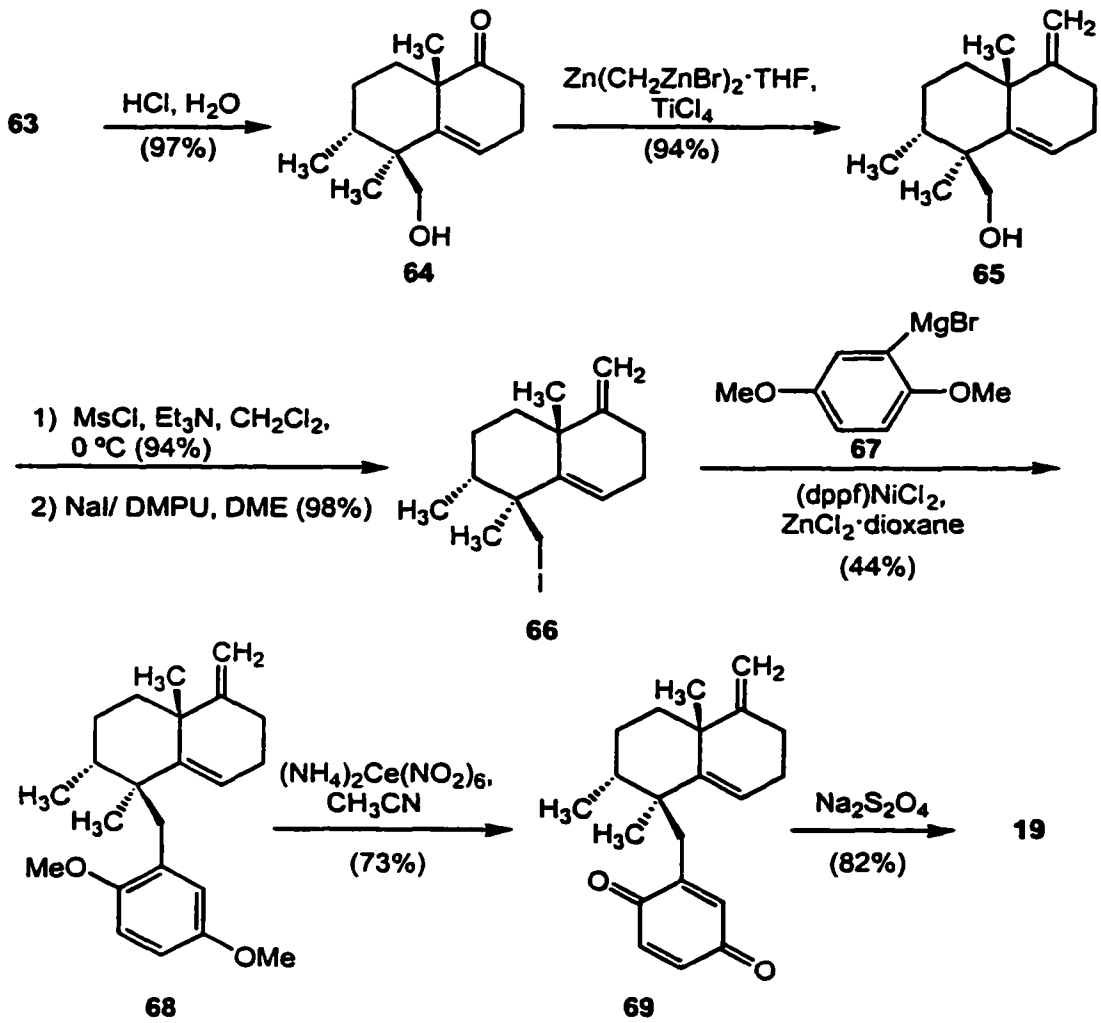
Wiemer's approach to the synthesis of (±)-arenarol **19** utilized a nickel- mediated coupling at a neopentyl center and the directed hydrogenation of an unsaturated neopentyl alcohol to provide the stereocontrolled formation of two adjacent tertiary centers (Schemes IX and X).[33] The decalin core was prepared by the reaction of 2-



Scheme IX

methyl-1,3-cyclohexanedione **57** and Nazarov's reagent (ethyl 3-oxo-4-pentenoate) to give the diketone **58**. Subsequent protection of the isolated ketone provided **59**, which under deconjugating conditions was methylated to provide the olefin **60**. Nysted's reagent was used to introduce an exocyclic methylene followed by $LiAlH_4$ reduction of the ester to provide the desired neopentyl alcohol **62**. Hydrogenation of the exocyclic double bond of **62** with $[Ir(cod)(Pcy_3)(py)]PF_6$ gave a single diastereomer **63** presumably based upon the complexation of the alcohol to the catalyst.

The dioxolane protecting group of **63** was removed by treatment with aqueous acid and treatment of the resulting ketone **64** with Nysted's reagent gave the desired olefin **65** (Scheme X). Homologation of the hydroxyl group into the corresponding iodide using a two-step sequence (MsCl, Et_3N; NaI) gave **66**. Coupling of the derived Grignard reagent **67** to **66** in the presence of $(dppf)NiCl_2$ and $ZnCl_2$•dioxane provided **68** in modest yield (44%). Deprotection of the methyl ethers with simultaneous oxidation of the resulting phenols provided (±)–avarone **69** that was reduced under mild conditions to provide (±)–arenarol **19**.

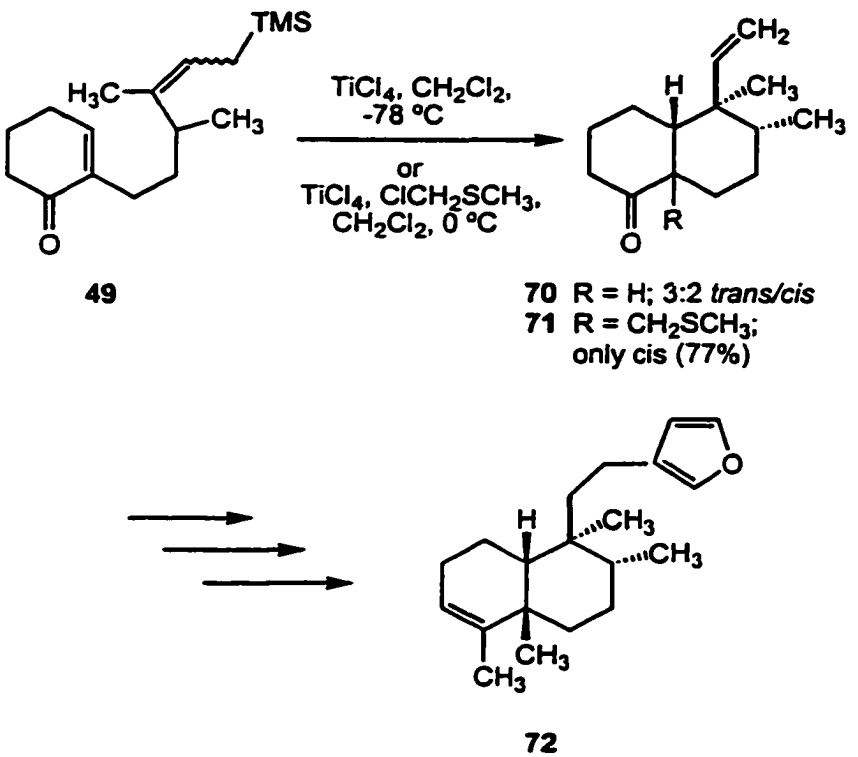


Scheme X

Decalin Synthesis

The synthesis of the *cis*-decalin framework contained within the *cis*-clerodanes is particularly challenging due to the need to construct contiguous stereogenic centers. To date most clerodane syntheses have been lengthy, in part, due to the installation of the stereochemical features after the decalin core has been generated, usually via a variation of the Robinson annulation. The congestion of the stereogenic carbon centers limits the kind of transformations available, thus making it desirable to utilize diastereoselection in these synthetic processes. Preferred methods typically involve face-selective reactions, conformational equilibration, and stereoselective cyclization reactions. Generally, with face-selective reactions and equilibration reactions, the syntheses involve the step-wise introduction of the stereogenic centers and are less convergent and quite lengthy.

More efficient cyclization reactions allow ring formation and the stereoselective introduction of stereogenic centers to occur at the same time. One notable synthesis of this type was reported by Tokoroyama in the synthesis of the *cis*-clerodane linaridial **72** (Scheme XI).[32] An intramolecular Hosomi-Sakurai cyclization on **49** gave an intermediate enolate that provided a mixture of decalins **70** upon protonation. This mixture could be epimerized to form the *trans*- product exclusively or the enolate could be trapped with chloromethyl methylsulfide ($ClCH_2SCH_3$) to form the *cis*-fused **71**. While compound **71** was easily converted to linaridial **72**, the application of this methodology to other *cis*-clerodanes would require tedious functionalization processes.



Scheme XI

The Diels-Alder reaction is a method of generating substituted cyclohexenes from the cycloaddition of a diene **73** and a dienophile **74** (Figure 9).[34] The mechanism is concerted and requires that the diene adopt the *s-cis*-conformation for the transformation to occur and that the diene and the dienophile approach each other along approximately parallel planes.

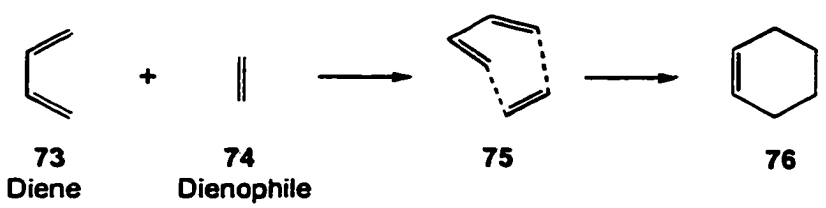


Figure 9

If the dienophile is unsymmetrical, two possible products exist (Figure 10). The dienophile can approach the diene in an *endo*-orientation in which the substituent X on the dienophile is oriented toward the π orbitals of the diene to give **78** or in an *exo*-orientation in which the substituent X is directed away from the π system to provide cyclohexene **80**. Either product may exist, but the Alder rule states that the *endo* mode is usually preferred when an unsaturated substituent, such as a carbonyl, is present due to the favorable interaction between the dienophile substituent and the π electrons of the diene, commonly referred to as secondary orbital overlap.

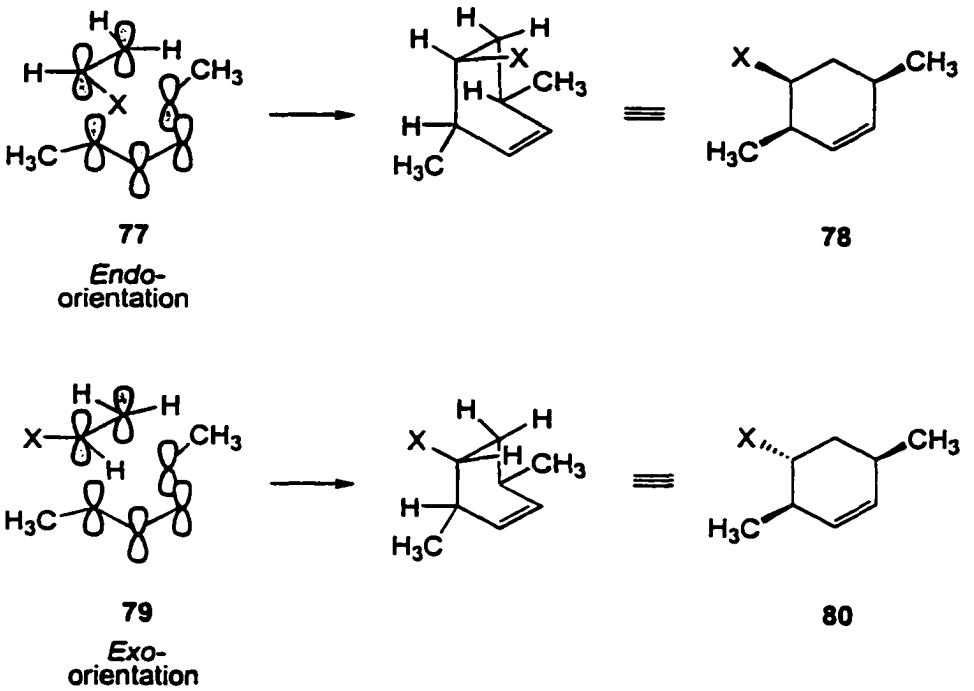


Figure 10

The intramolecular Diels-Alder (IMDA) cyclization is commonly used for the construction of decalin ring systems where both six-membered rings of the decalin skeleton are formed simultaneously from an acyclic precursor. However, the

stereochemical outcomes of the cyclizations are not always predictable when a tether connects the diene to the dienophile. Frequently, as in Roush's study (Figure 11),[35] a mixture of stereoisomers is formed that may reflect a conflict between the Alder rule favoring *endo*-addition and the conformation of the tether that favors the *exo*-transition state. Substituents present within the system also may affect the outcome of the reaction, and currently, no general rules for the stereoselectivity of the IMDA cyclization have been put forward.

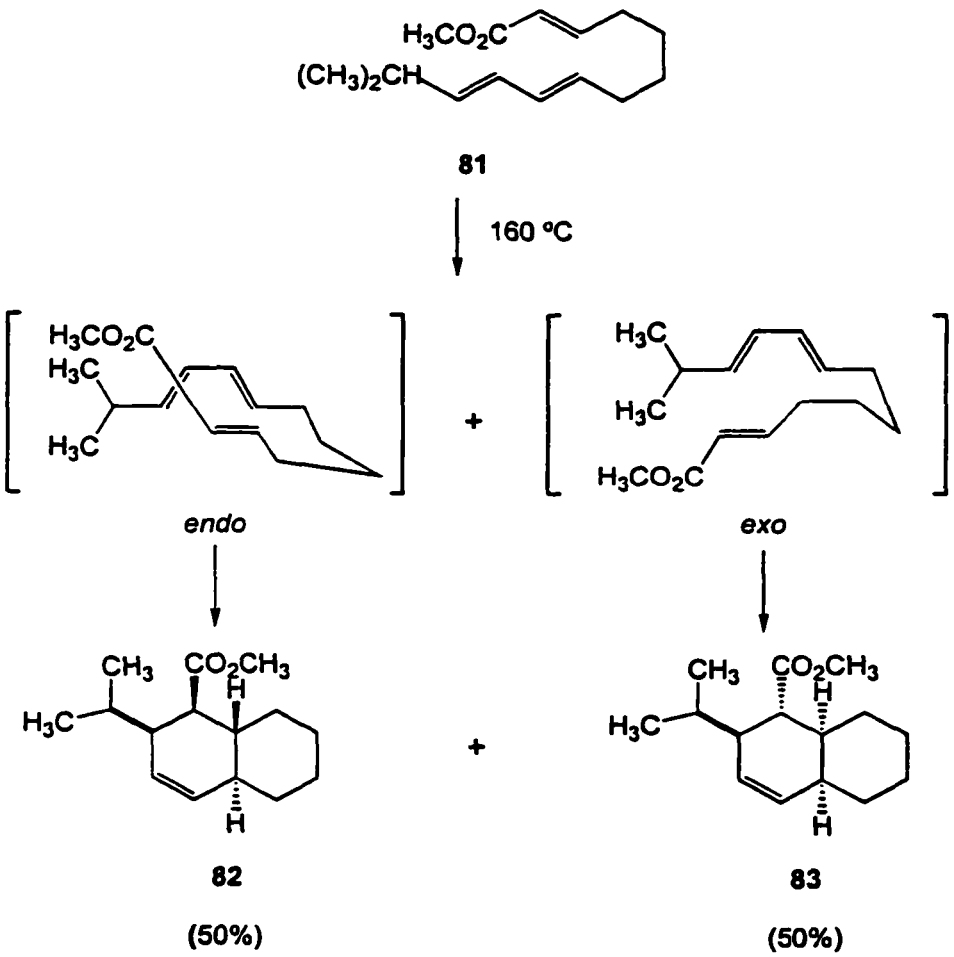
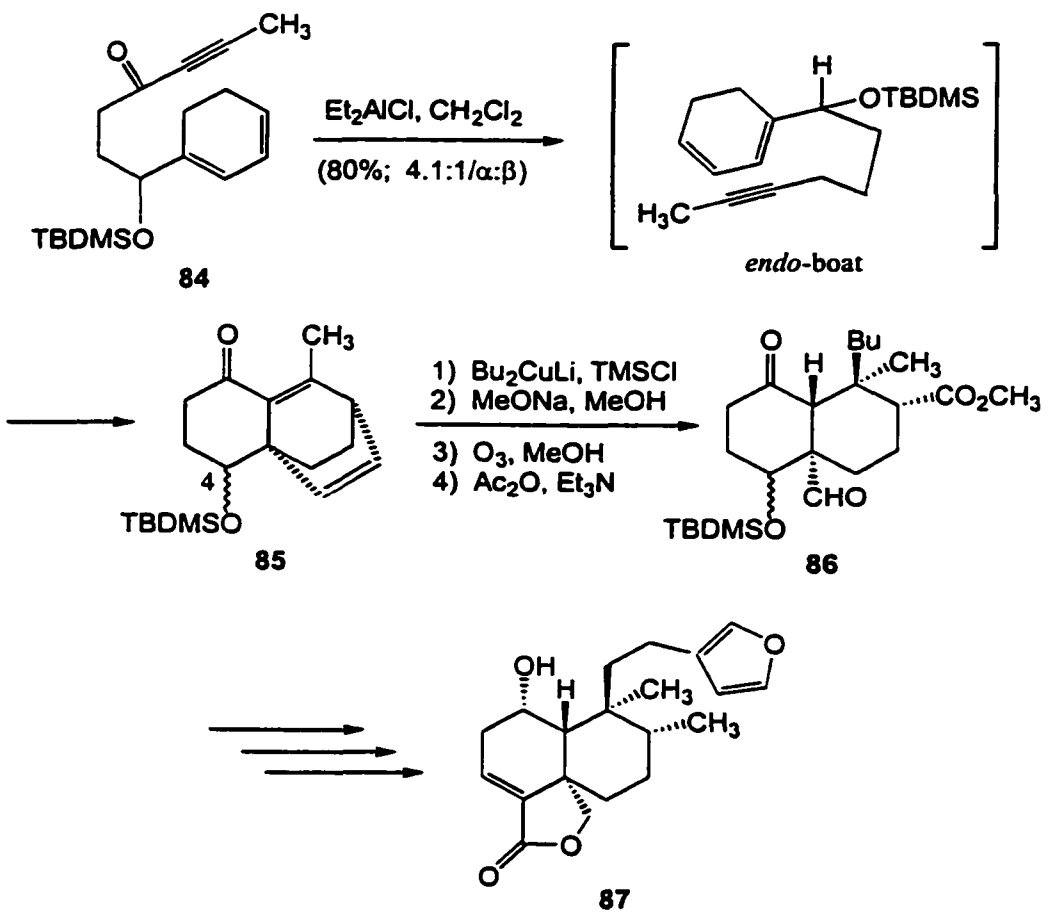


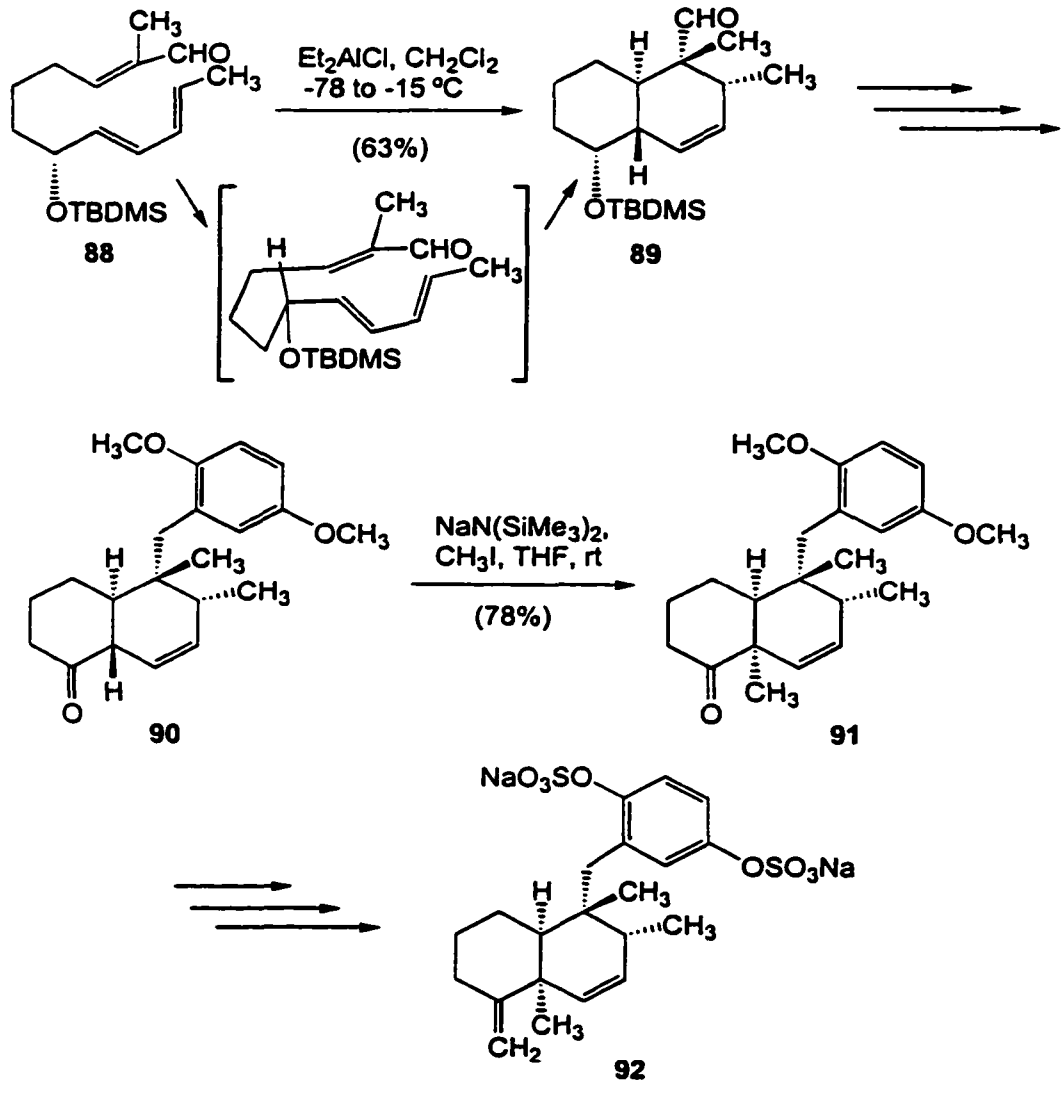
Figure 11

To date, the application of the IMDA cyclization for the construction of the clerodane skeleton has been used by Taschner[36] to synthesize bacchofertin **87** (Scheme XII) and by Kobayashi[37] to synthesis a model drimane compound **92** (Scheme XIII). Taschner's method uses the IMDA reaction with the acetylenic ketone **84** which provided the tricyclic product **85** in good yield, but as a mixture of epimers at C-4. Conjugate addition to **85** followed by oxidative ring opening produced decalin derivative **86** with the *trans*-clerodane skeleton that was subsequently converted to bacchofertin **87**.



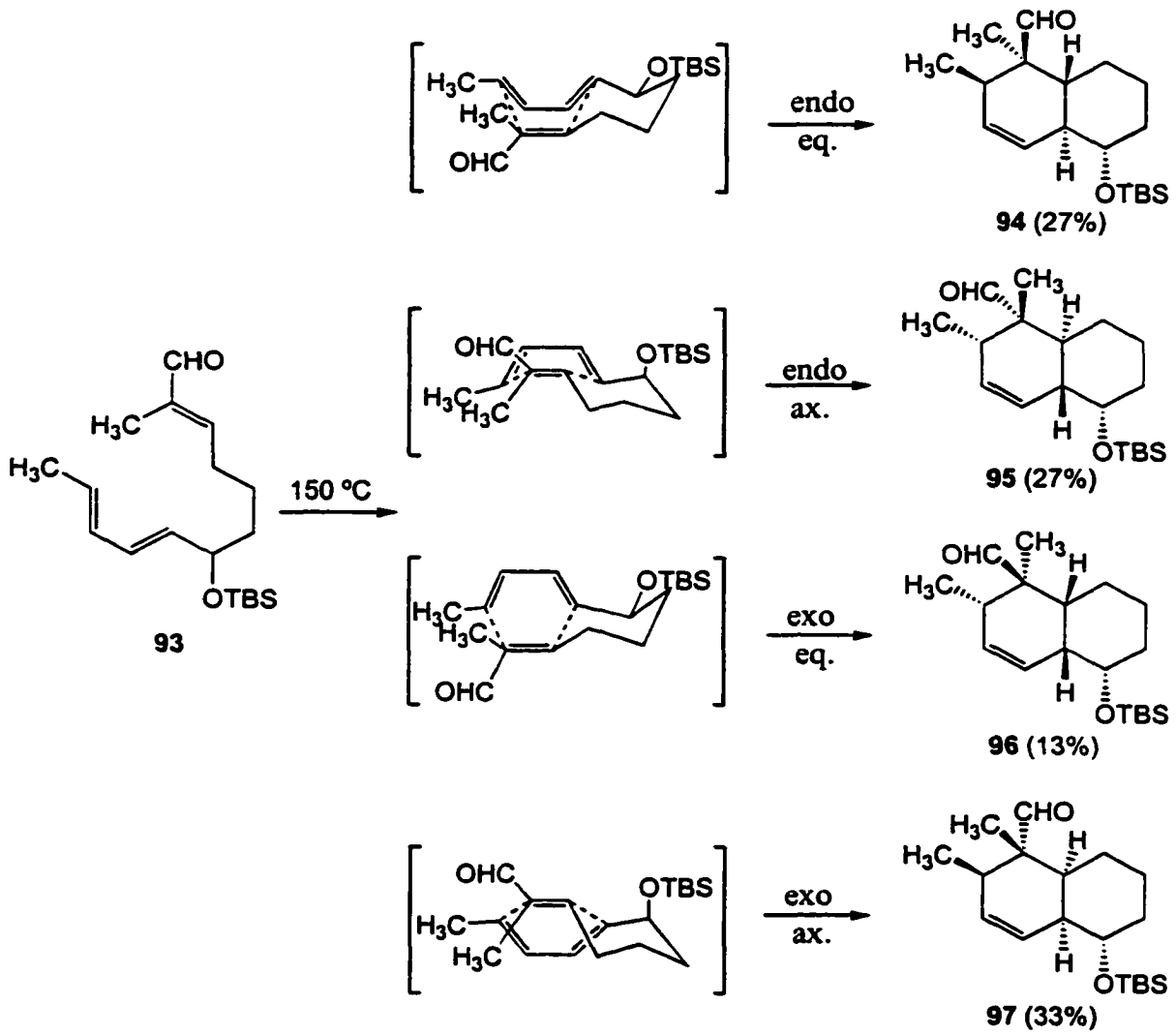
Scheme XII

Kobayashi performed a Lewis acid mediated IMDA cyclization on **88** to afford the *trans*-decalin **89** with the 8,9-*trans*-dimethyl arrangement (Scheme XIII) via an *endo*-boat intermediate. Stereoselective methylation using $NaN(SiMe_3)_2$ / methyl iodide installed the angular methyl and epimerized the decalin to the *cis*-configuration, **91**, from which the target compound **92** was readily prepared.



Scheme XIII

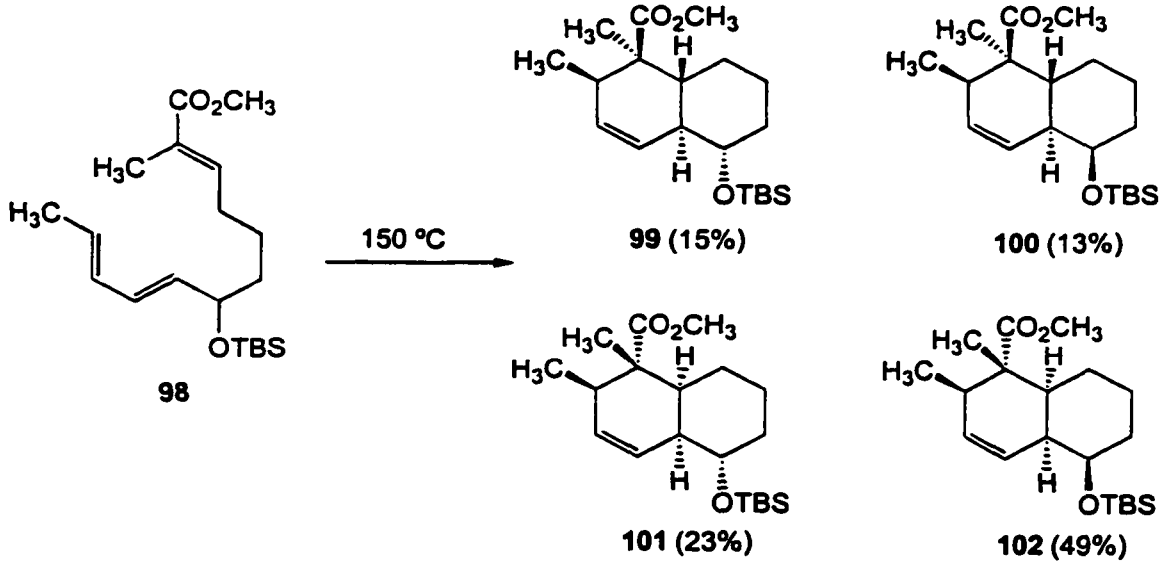
Several Diels-Alder studies on the preparation of the decalin systems have shown that structural features present in the tether can determine the stereochemical outcome of the cycloaddition. In particular, the thermal cycloaddition of the 7-substituted-2,8,10-undecatrienal **93** yielded predominantly *trans*-fused decalins **94** and **95** (Scheme XIV). They were believed to arise from an *endo*-oriented diene with respect to the dienophile.[38] The tether can occupy a chair conformation during the



Scheme XIV

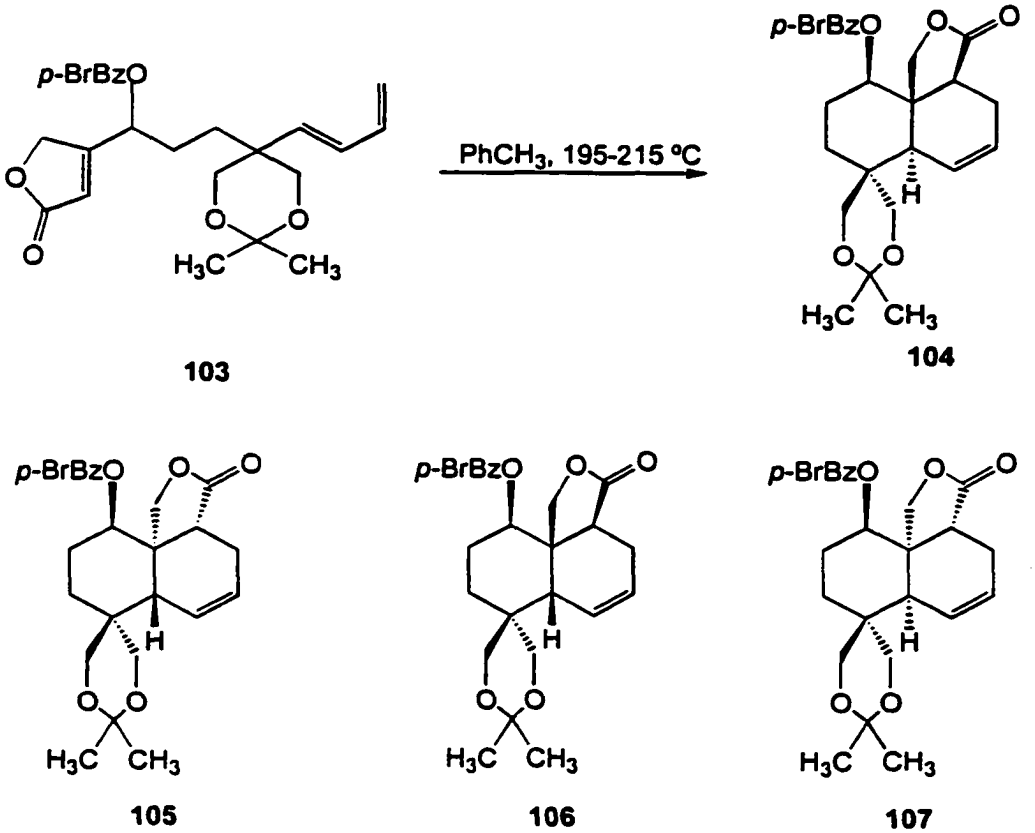
transformation for both the *exo*- and *endo*-configuration and the *cis*- and *trans*-products result from the silyl ether substituent residing in either an equatorial or axial position.

In a similar study, Roush[39] reported that the cyclization of substituted 1,7,9-decatrienoate **98** yielded *cis*-fused decalins **101** and **102** as the major products and not the anticipated *trans*-decalins **99** and **100** (Scheme XV). Although the Alder rule suggests that an *endo*-orientation of the dienophile with respect to the diene should provide *trans*-fused products, the actual product distribution implies that an *exo*-orientation takes place during the transition of the IMDA cyclization and that overall, secondary orbital overlap does not control the stereochemical outcome of the reaction. Removable directing groups incorporated on the tether have also shown varying degrees of success at directing the stereocontrol of the IMDA reactions.[40,41]



Scheme XV

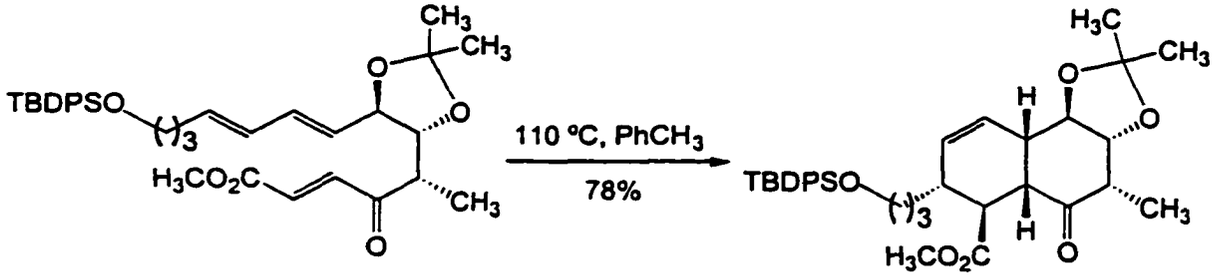
Varying the dienophile configurations and other structural features on the tether have also been examined as a means to predict the formation of *cis*-fused or *trans*-fused decalins. In a report by Murai,[42] a butenolide dienophile with a secondary benzoate ester adjacent to it was found to give a predominance of *trans*-fused decalin products that were believed to arise from chair-like transition states (Scheme XVI). These results implied that allylic quaternary centers coupled with cyclic dienophiles favor *trans*-fused products from chair-like transition states. The selectivity, however, was not high.



Product ratio: 59/15/24/2

Scheme XVI

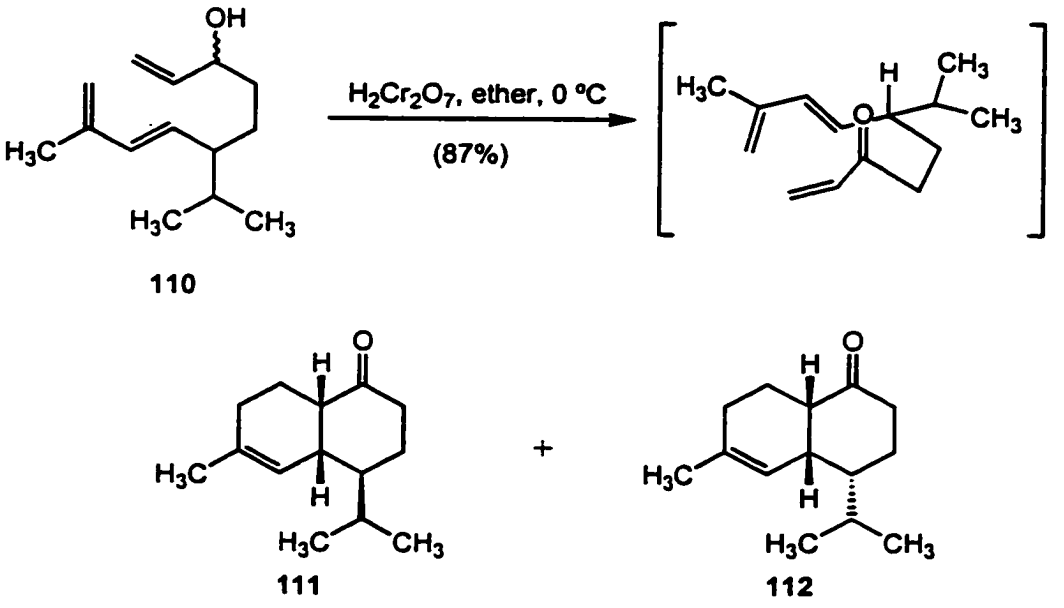
In Roush's [43] and Taber's[44] studies, the incorporation of a carbonyl in the tether was shown to have a significant effect on the outcome of the cyclization. The cyclization of substituted 1,7,9-decatrien-3-one **108** yielded the *cis*-fused decalin **109** which Roush suggested was based on a boat-like transition state (Scheme XVII).



108 **109**

Scheme XVII

Taber's study also showed that the introduction of a carbonyl in the tether could favor a boat transition state, which was alleged to be more stable (Scheme XVIII) and provide a *cis*-fused decalin. When the alcohol **110** was oxidized, spontaneous cyclization occurred to provide a 9:1 mixture of *cis*-fused decalins **111** and **112** in high yield (87%). The isopropyl substituent prefers the equatorial position and the product distribution reflects that preference.



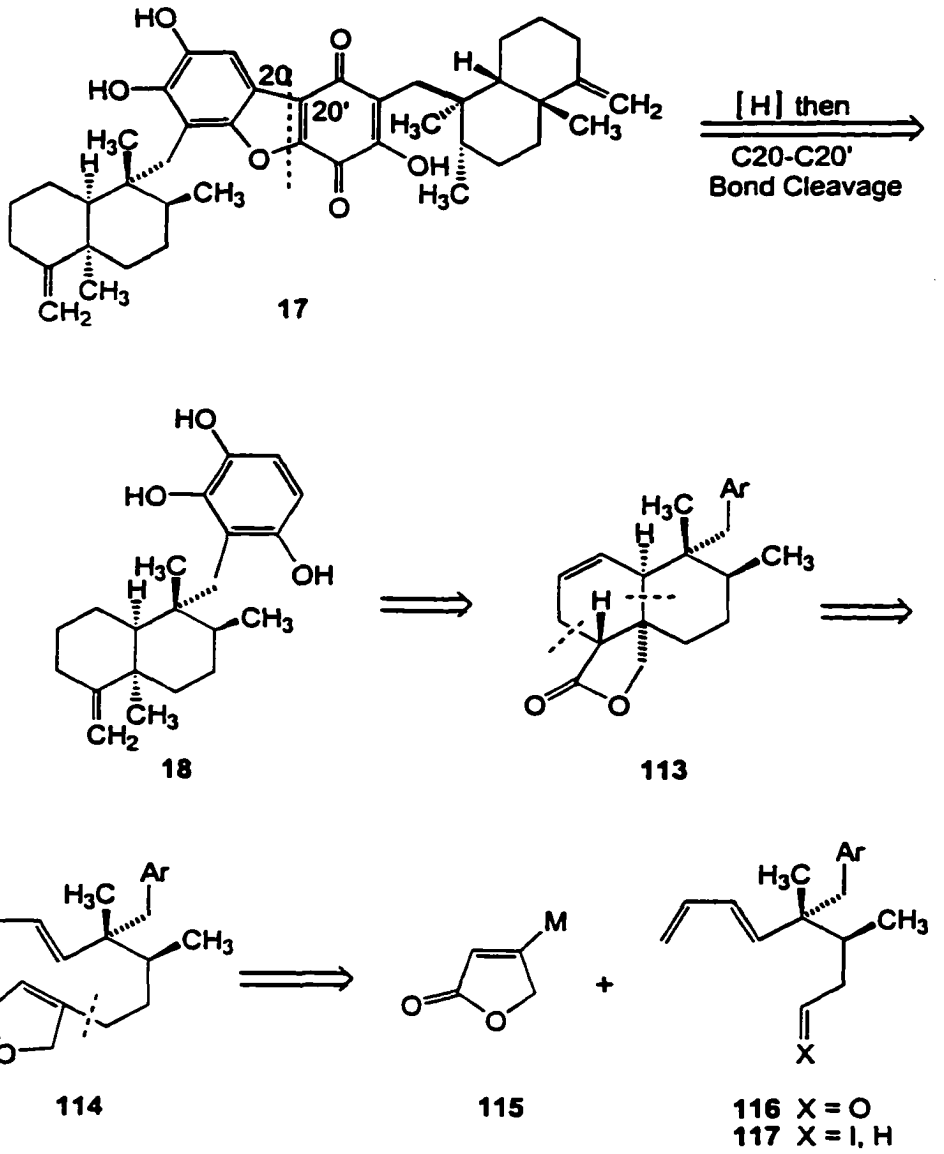
9 / 1

Scheme XVIII

Analysis

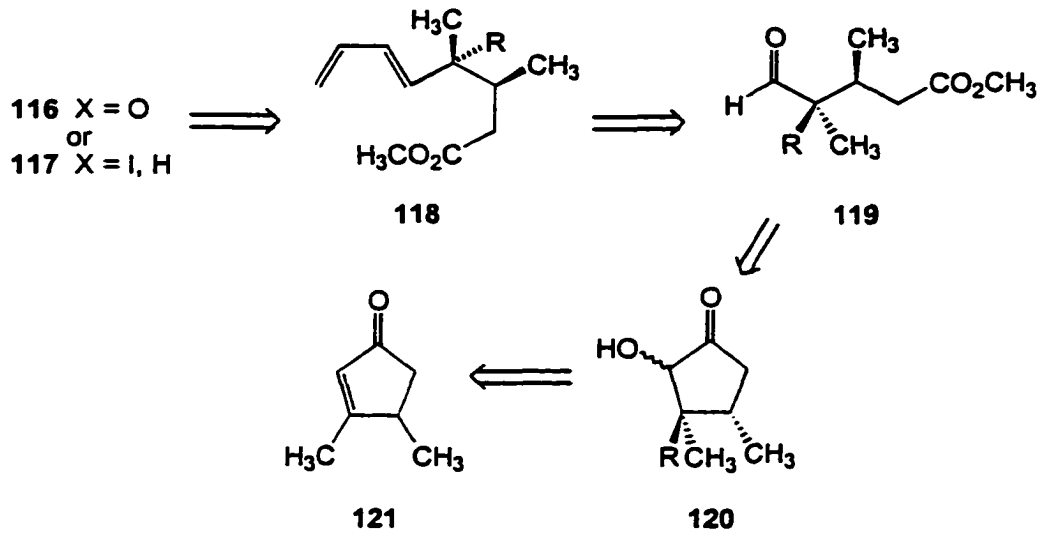
Our strategy for the synthesis of the natural product, popolohuanone E **17**, was to divide it into 2 identical monomers **18** each consisting of a *cis*-decalin portion and a substituted aromatic ring (Scheme XIX). Two aspects of this approach were investigated: i) the preparation of the aromatic core by developing methodology to synthesize suitably substituted dibenzofurans that would be used to put the two monomers together (Scheme XXII, Chapters 1 and 2) and ii) methods to synthesize the *cis*-decalin framework (Schemes XX – XXI, Chapter 3).

For the preparation of the *cis*-clerodane portion, 6'-hydroxyarenarol **18** was envisioned to arise from decalin **113** via standard transformations (Scheme XIX). Decalin **113** would be prepared by the Diels-Alder cyclization of triene **114**, a process that is anticipated to provide the desired *cis*-stereochemistry. The triene would be prepared by the addition of butenolide **115** to either the aldehyde **116** or the iodide **117**.



Scheme XIX

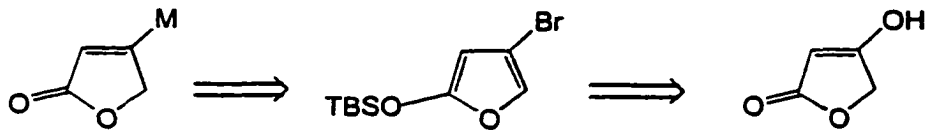
The addition substrates **116** and **117** could be accessed from the corresponding ester **118** that could in turn be prepared by homologation of aldehyde **119** (Scheme XX). A cuprate addition to dimethylcyclopentenone **121** followed by cleavage of the derived α-hydroxy ketone **120** would provide this aldehyde.



118 119 121 120

Scheme XX

The metallo-furanone **115** (butenolide) could be prepared as a synthon **122** from tetronic acid **123** (Scheme XXI) *via* a process developed by Jas[45] in which tetronic acid was brominated and then converted into 2-*tert*-butyldimethylsilyloxy-4-bromofuran **122** by a two-step process.

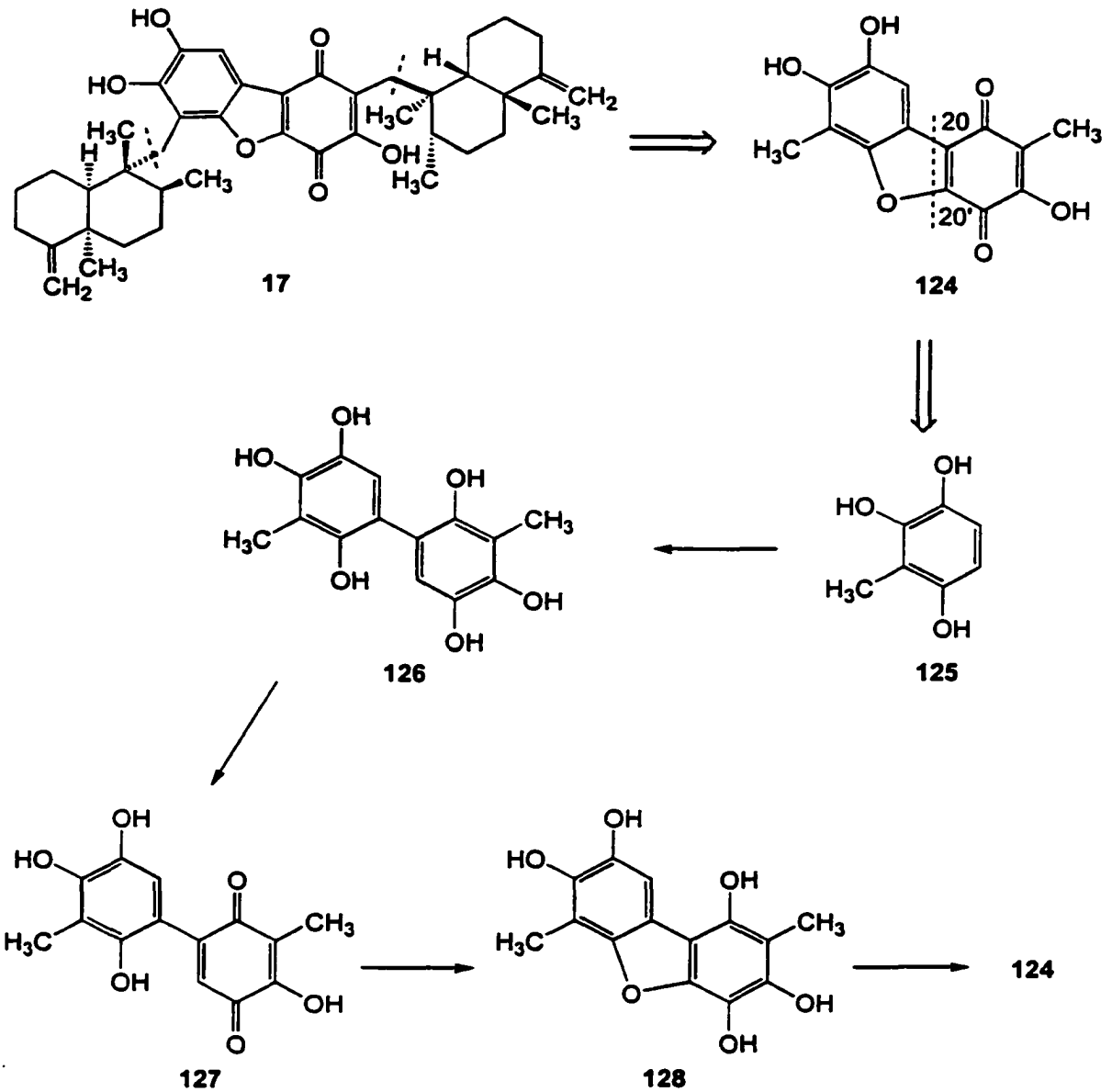


115 **122** **123**

Scheme XXI

As a model system for the end game for the synthesis of popolohuanone E the decalin rings can be removed from **17** to afford a simplified 1,4-dibenzofurano-quinone **124** (Scheme XXII). Reduction of the quinone portion of **124** and cleavage adjacent to bonds C20-C20' (numbering of the natural product) provides the hydroxylated aromatic **125**. In the forward reaction, an oxidative coupling between the two arenol monomers

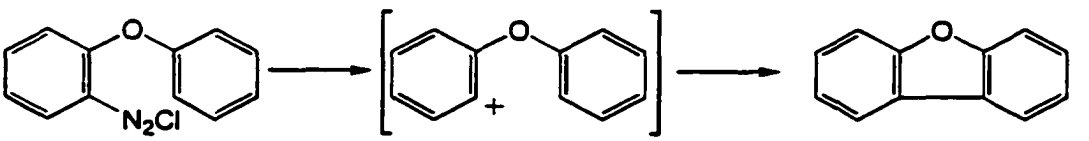
would give biaryl **126** in which one of the 1,4-quinones could be selectively oxidized to provide the hydroxyquinone **127**. A subsequent intramolecular Michael addition of the hydroxyl group adjacent to the biaryl linkage into the quinone would produce the furan ring of **128** and another oxidation of the 1,4-dihydroquinone would provide the model **124**.



Scheme XXII

Results and Discussion

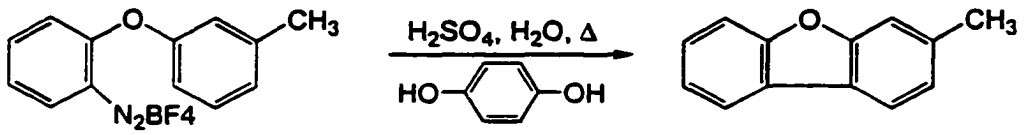
Currently, the methodology for the generation of dibenzofurans is limited. One classical method, the Pschorr reaction,[46] generates dibenzofurans from diazonium salts via an ionic mechanism (Figure 12). The reaction may be performed under basic or acidic conditions. In a typical reaction, a diazonium salt such as **129** is decomposed in acid and in the presence of copper powder to provide a carbocation **130** that cyclizes to the dibenzofuran **131** in modest yield (<45%). This is most likely due to the highly reactive diazonium salt, and multiple side reactions that compete with the cyclization.



129 **130** **131**

Figure 12

Recently, Wassmundt *et al.*[47] reported a modified procedure that uses promoters like hydroquinone, $FeSO_4$, $SnCl_2$, NaI, or $CuSO_4$ to increase the yields of dibenzofurans (>70%). The mechanism is proposed to occur by a free-radical pathway in which hydroquinone serves as an electron source. An aqueous suspension of the diazonium salt **132** containing an equimolar amount of sulfuric acid is added dropwise to an equimolar amount of the promoter in boiling water to afford the dibenzofuran **133** in high yield (Scheme XXIII).



132 133

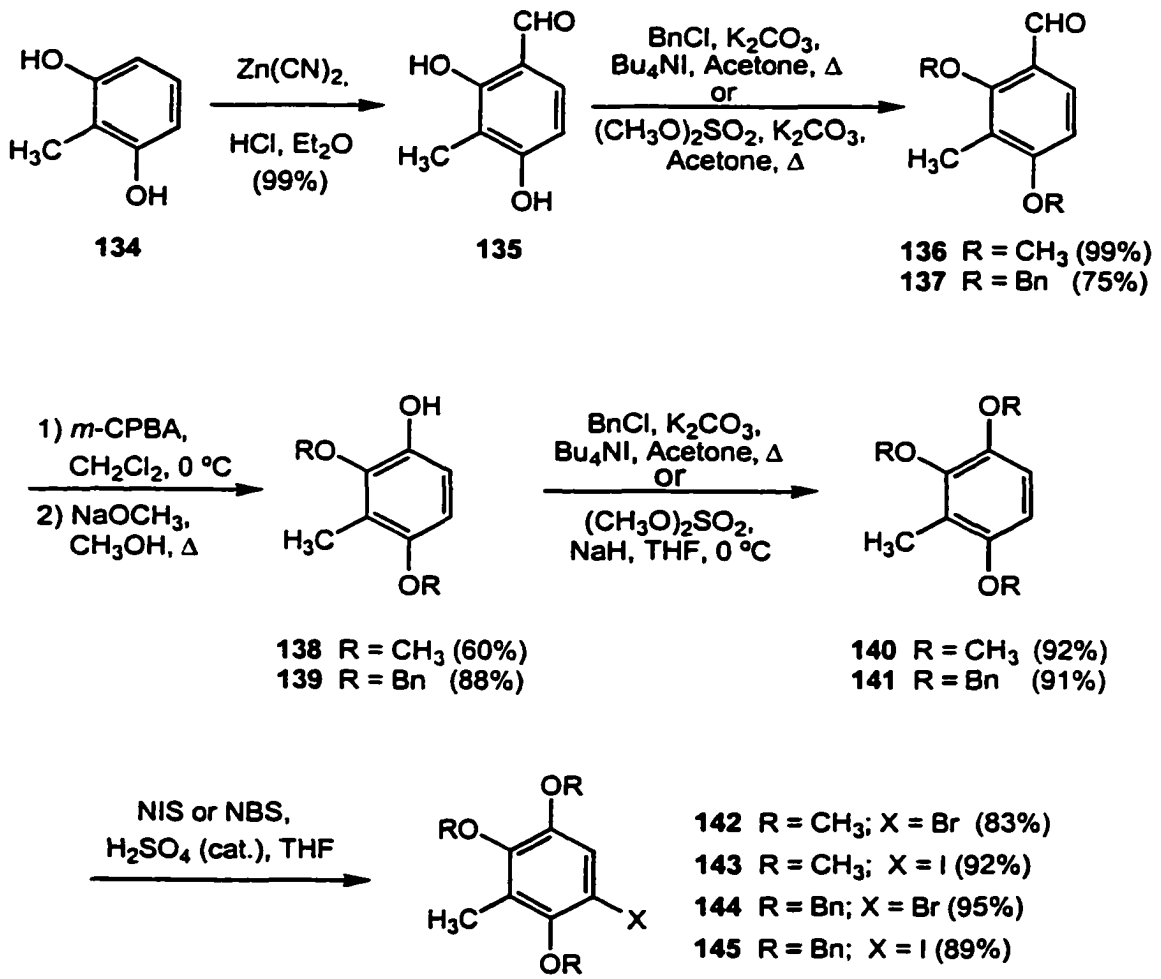
Scheme XXIII

However, even with Wassmundte's improvement, the methodology suffers. The harsh reaction conditions do not tolerate many functional groups and the cyclization requires a biaryl ether which itself is not easily prepared in high yield by the standard Ullman reaction.[48]

With these conditions in mind, the first challenge in the synthesis of the dibenzofuran-1,4-dione heterocycle **124** was to prepare a biaryl linkage from two identical arenols. The majority of coupling techniques used to form biaryls employ transition metals to couple aryl halides and metallobenzenes; ferric chloride,[49] nickel[50,51] and copper[52] catalysts and a large number of palladium[53-55] catalysts can be utilized with a variety of aromatic substrates including aryl halides, aryl stannanes and aryl triflates. Most of these coupling procedures require an aryl halide, and would not tolerate the hydroxyl functionality needed for our synthesis. Therefore, the preparation of suitably protected aryl halides was undertaken.

The preparation of permethylated and perbenzylated protected phenols began with 2-methyl resorcinol **134** (Scheme XXIV). Formylation via the Gatterman procedure[56] provided aldehyde **135** that was *O*-alkylated to produce dimethoxybenzaldehyde **136** or dibenzyloxybenzaldehyde **137**. Baeyer-Villiger oxidation[57] with *m*-chloroperoxybenzoic acid (*m*-CPBA) and saponification of the intermediary formates in warm sodium

methoxide/methanol afforded the phenols **138** and **139**. Subsequent protection of the phenols with dimethyl sulfate (NaH, THF) for the methoxy case[58] or with benzyl chloride (*n*-Bu_4NI, K_2CO_3, acetone) for the benzyloxy series[59] yielded derivatives **140** and **141**, respectively. Halogenation could be achieved with an *N*-halosuccinimide (NBS[49]) or (NIS[60]) and supplied the trimethoxy derivatives **142** and **143** and the tribenzyloxy halides **144** and **145**.



134

135

136 R = CH_3 (99%)
137 R = Bn (75%)

138 R = CH_3 (60%)
139 R = Bn (88%)

140 R = CH_3 (92%)
141 R = Bn (91%)

142 R = CH_3; X = Br (83%)
143 R = CH_3; X = I (92%)
144 R = Bn; X = Br (95%)
145 R = Bn; X = I (89%)

Scheme XXIV

Having the precursors in hand, several methods were assayed for the coupling of the aryl halides to form biaryls. The trimethoxy halides were subjected to ferric chloride[49] treatment ($FeCl_3/CH_3CN$), but the yield of coupled material was low (<25%) and the reaction was erratic. Frequently, starting material was recovered unchanged. The condition of the catalyst may have been the main problem: inadvertent exposure to air would lead to contamination by material possessing several different oxidation states. Subjecting the tribenzyloxy halides to the same reaction conditions gave similar results (coupling <10%), but upon prolonged stirring at reflux, a new material was isolated in which coupling had also occurred between the benzyl protecting groups in low yield (<10%). Under these reaction conditions, the coupling was indiscriminate in that not only was the desired product obtained, but also new material was isolated in which coupling had occurred between the aryl halides and the benzyloxy protecting groups.

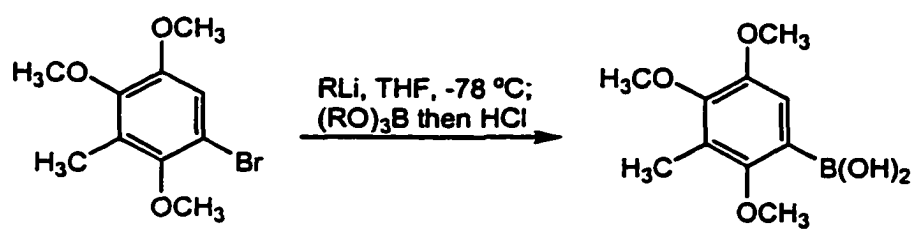
The use of copper or nickel catalysts or the palladium-mediated couplings of magnesium or lithium anions also proved difficult in our hands. For most of the aryl halides, the lithium anion formation was monitored by TLC analysis in which there existed a clear difference between the R_f values of the aryl halide and the protonated aromatic. However, the resulting aryl anion was very sensitive to additives, and the couplings failed. Achieving and maintaining an oxygen free environment was believed to be the source of these difficulties.

The Suzuki coupling[61,62] of aryl boronic acids with aryl halides proved to be one method that gave reproducible quantities of coupled aromatics. Initially, the procedure of Keay[63,64] was utilized for the formation of the biaryl linkage. This procedure involved generating the boronic acids and performing the coupling procedure *in situ*. Yields of

coupled material were low (<20%), which may have been due to interference by small amounts of phenolic by-products that arise during the formation of the boronic acid. Purification of the aryl boronic acids by chromatography was necessary prior to the coupling procedure.

These boronic acids were prepared from the corresponding aryl halides by metal-halogen exchange with 2.2 equivalents of alkyl lithium followed by quenching with tri-*O*-methyl borate and acid hydrolysis. The alkyl lithium of choice was *s*-BuLi for the trimethoxy series (Table 1). The yields were lower with *n*-BuLi. Since the by-product obtained from using *n*-BuLi was the "protio" **140**, the aryl lithium generated during the exchange may have quickly abstracted a

Table 1



142 **146a**

Run	Alkyl Lithium	$(RO)_3B$	Boronic Acid **146a** (%)
1	*n*-BuLi	$(CH_3O)_3B$	8
2	*s*-BuLi	$(CH_3O)_3B$	41
3	*t*-BuLi	$(CH_3O)_3B$	-
4	*s*-BuLi	$[(CH_3)_2CHO]_3B$	72

proton from an undetermined source even before the trialkyl borate was added. No exchange occurred with *t*-BuLi, most likely due to the steric congestion around the halide (Figure 13).

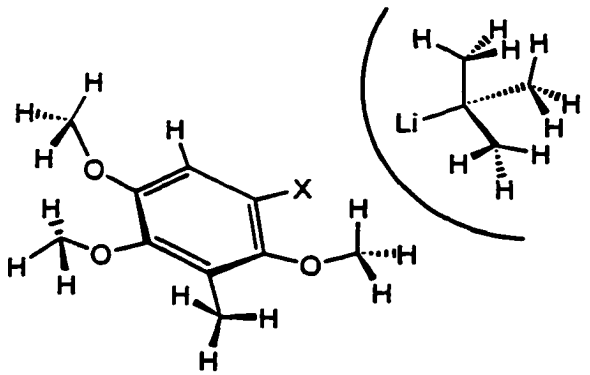


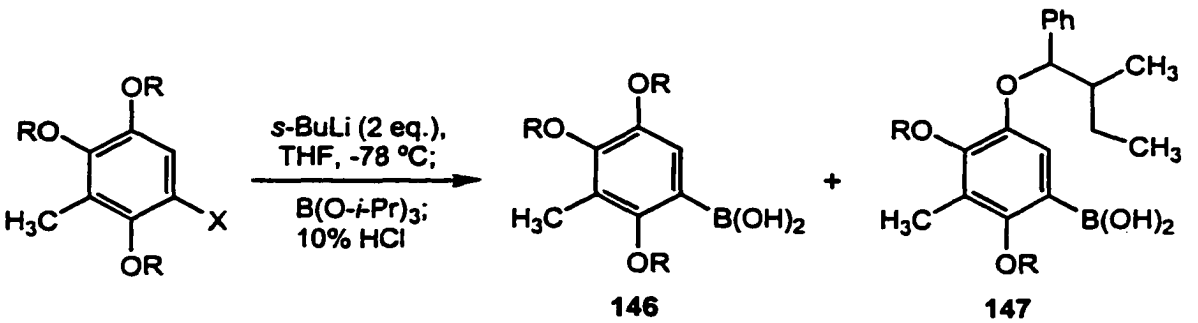
Figure 13

Quenching the anion generated by metal-halogen exchange of **142** with tri-*O*-methyl borate followed by acid hydrolysis provided the boronic acid in low yields (41%). Even with freshly distilled tri-*O*-methyl borate a fair amount of "protio" was obtained. The use of tri-*O*-isopropyl borate[65] instead of tri-*O*-methyl borate was also investigated to further improve upon the yields of the boronic acids. Freshly distilled tri-*O*-isopropyl borate dramatically improved the yield of the boronic acid products that were obtained as stable solids (Table 1).

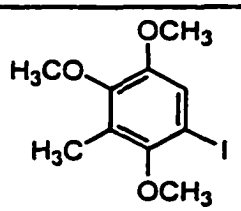
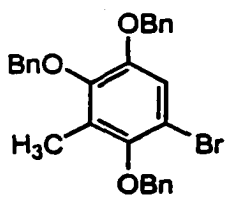
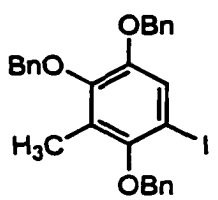
The choice of the aryl halide for anion formation was also investigated. The aryl bromide and aryl iodide series provided aryl boronic acids in all cases using standard conditions, but whereas aryl iodide **145** provided boronic acid **146d**, the corresponding aryl bromide **144** provided a 2.5:1 mixture of products (Table 2). Alkylation on the C3

benzylic position was suspected to have occurred to provide boronic acid **147c**. This result raised several questions: i) why did this benzyl ether undergo the alkylation? ii) why had this occurred with the tribenzyloxybromide **144** and not the tribenzyloxyiodide **145**? and iii) was this a specific case or of a general nature?

Table 2



146 **147**

Run	Substrate		146 (%)	147 (%)
b		**143**	63	-
c		**144**	57	22
d		**145**	76	-

A comparison of the ^{1}H NMR spectrum of the new boronic acid **147c** with that from **146d** provided some insight as to what was occurring in the reaction. It was clear that an addition of an alkyl chain had occurred and that one of the benzylic positions had been altered; one benzylic singlet (δ 5.06 ppm) had become a doublet (J = 6.6 Hz) integrating for only 1H while another benzylic position (δ 5.29 ppm) appeared as an AB spin pattern (Figure 14). In order to obtain this product a dianion had to have formed during the reaction. Also, the only possible source of an electrophile prior to the addition of the borating agent was the *s*-butylbromide (*s*-BuBr) generated during the lithium-halogen exchange.

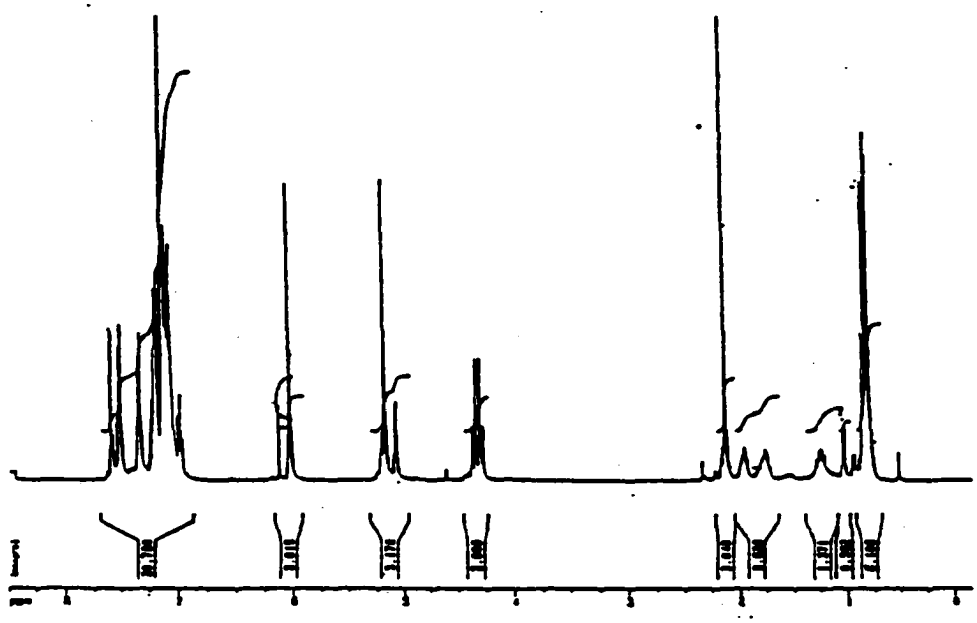


Figure 14

The major difference between the methoxyl and the benzyloxy series is the increased steric congestion on the ring for the tribenzyloxy cases (Figure 15).[66] During the halogen-metal exchange, the lithium counterion chelates with both the C6 oxygen and

two solvent molecules. The C6 benzylic protons should rotate away from this bulky chelate toward the opposite side of the molecule, thus making them inaccessible to deprotonation by base. The C2 benzylic protons are flanked on both sides by bulky groups (a methyl group and another benzyloxy group) which makes them less accessible to base. Also, the relative acidities of the available protons becomes a significant factor for the product obtained. The protons attached to the core aromatic ring and those attached to the aromatic rings of the protecting groups have a pk_a value of 43, making them too basic for possible metalation.[67a] All of the other protons available are in benzylic positions and have a pk_a value of 37.[67b] They are the next most acidic protons available in this system and are reactive toward lithiation because of the resonance stabilization of the resulting anions.[68] Therefore, metalation occurs at this site with the most available protons of the C3 benzyl ether to form a dianion that is alkylated with *s*-BuBr and gives the product after reaction with the triisopropylborate.

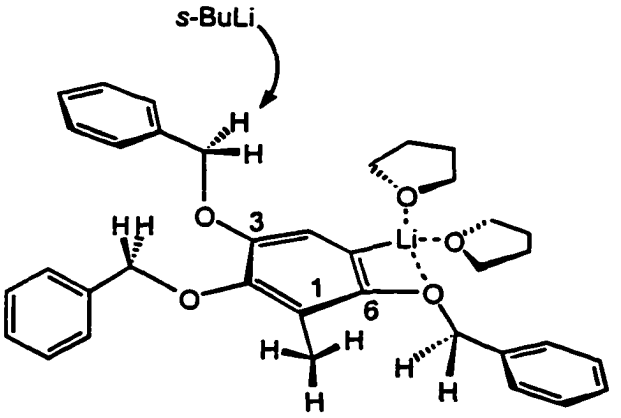
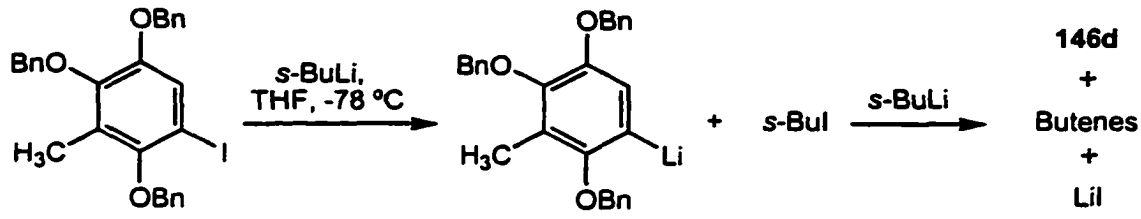


Figure 15

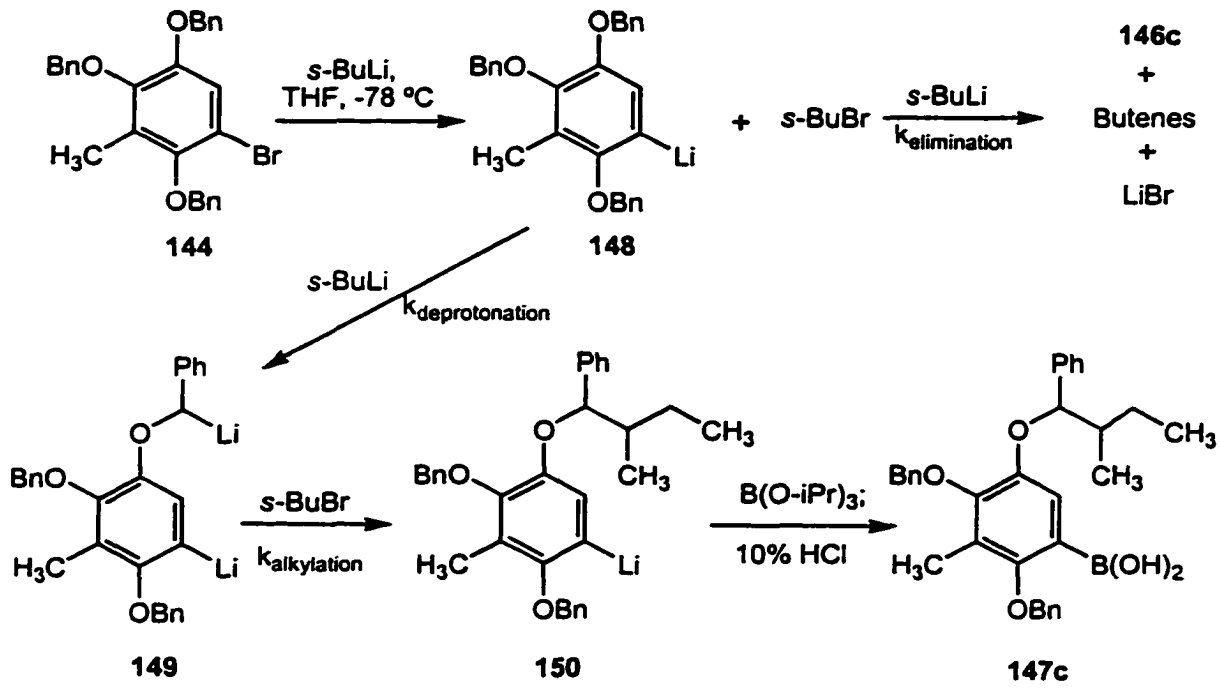
In the case of aryl iodide **145**, treatment with two equivalents of base leads to metal halogen exchange to form aryl anion **148** and generates *s*-butyliodide (*s*-BuI)(Scheme XXV). The second equivalent of base destroys this alkyl halide by an elimination process to form a mixture of unreactive butenes and lithium iodide (LiI). The rate of halide elimination from *s*-BuI is thought to approach that of diffusion control.



145 **148**

Scheme XXV

The order of the reactivity of the halide leaving groups is $I^- > Br^-$ and is dependant on the strength of the halogen to carbon bond which is ~50 kcal for the C-I bond and ~ 70 kcal for the C-Br bond.[69] In the case of the aryl bromide **144**, the destruction of the *s*-BuBr generated during the course of the reaction is retarded and excess base would be present in the reaction. Two processes would compete, that of elimination ($k_{elimination}$) to form the butenes and that of deprotonation ($k_{deprotonation}$) to abstract another acidic proton forming dianion **149** (Scheme XXVI). The remaining *s*-BuBr could function as an electrophile and alkylate the highly reactive anion to produce anion **150**. Upon the addition of borate, boronic acid **147c** could be obtained. These processes occurred prior to the addition of the borating agent since no diboronic acid was obtained.

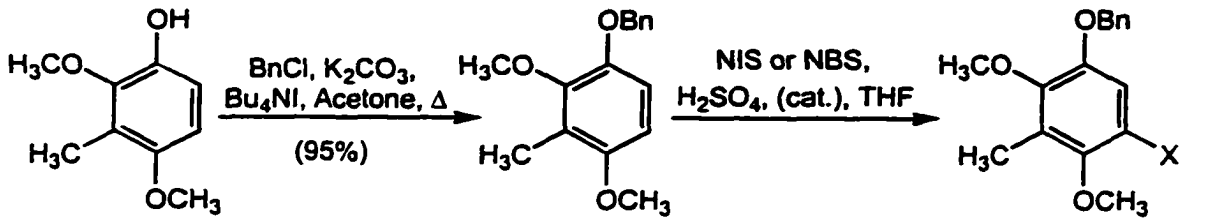


Scheme XXVI

The syntheses of differentially protected benzylic ethers were undertaken to elucidate this reaction. By systematically replacing the benzyloxy protecting groups with methoxy groups, the location of the protecting group that had undergone alkylation could be verified. This would also allow the scope of the process to be determined.

The differentially protected aromatics were prepared utilizing intermediates obtained along the original pathway (Schemes XXVII and XXVIII). The dimethoxyphenol **138** was benzylated at the C3 position and halogenated under the usual procedures to give aryl halides **152** and **153** (Scheme XXVII).

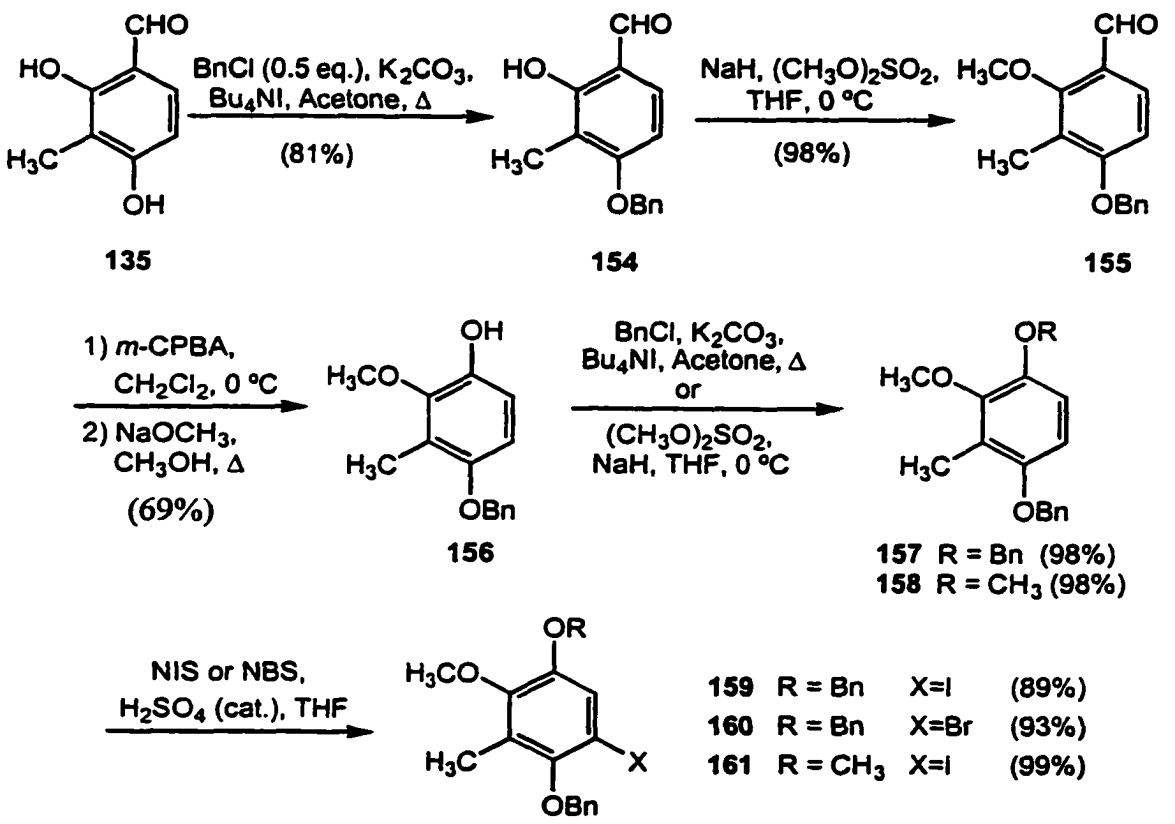
By limiting the amount of benzyl chloride (BnCl) to 0.5 equivalents in the initial protection step of **135**, mono-benzylation at the C6 position was achieved to provide **154**



138 **151** **152** X = I (89%)
153 X = Br (89%)

Scheme XXVII

(Scheme XXVIII). The protection of this phenolic position takes advantage of steric congestion experienced by the C2 phenol. Subsequent transformation to the *para*-dibenzyloxy halides **159** and **160** and to the mono-benzyloxy iodide **161** followed standard procedures.



135 **154** **155**

156

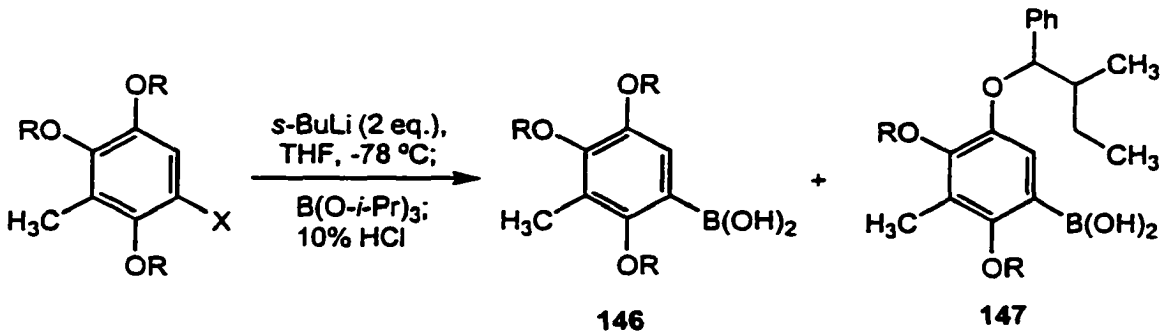
157 R = Bn (98%)
158 R = CH_3 (98%)

159 R = Bn X=I (89%)
160 R = Bn X=Br (93%)
161 R = CH_3 X=I (99%)

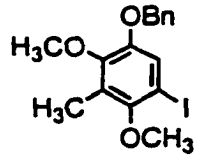
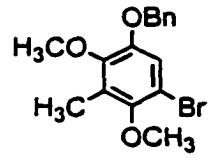
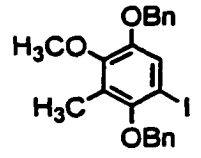
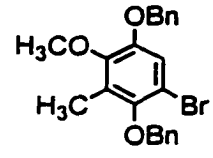
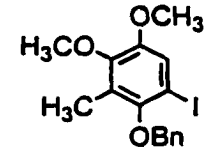
Scheme XXVIII

The aryl halides **152, 153, 159-161** were converted into the corresponding boronic acids (Table 3). Only a single boronic acid was obtained from the aryl iodides **152, 159,** and **161**. However, in the cases of the aryl bromides, a mixture of the desired boronic acid and the alkylated boronic acid was obtained in a ratio of 1:1 and of 3:2 for substrates **153** and **160**, respectively. The fact that bromide **153** showed alkylation at the benzyloxy protecting group (C3) strongly suggests that alkylation of **144** also occurred at the C3 ether. The dual alkylation that occurs suggests that there was an inherent problem with the aryl bromides series. It is clear that the aryl iodides were far superior substrates for the large-scale synthesis of the desired aryl boronic acid.

Table 3

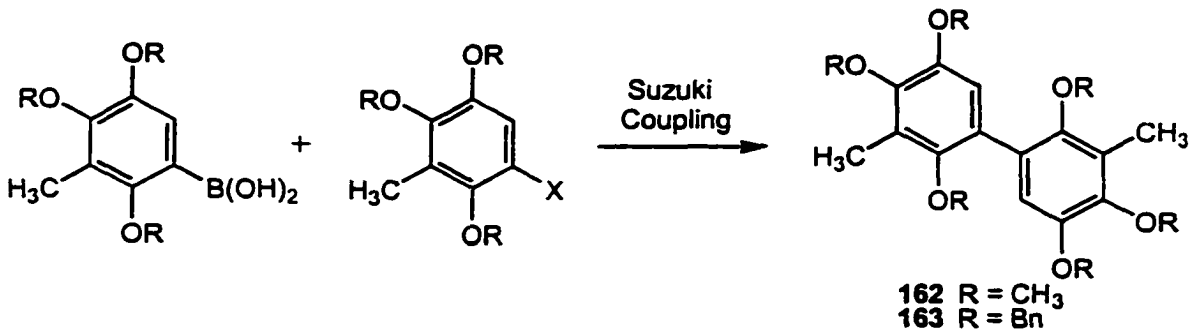


146 147

Run	Substrate		146 (%)	147 (%)
e		152	89	-
f		153	35	25
g		159	91	-
h		160	42	12
i		161	85	-

Several aspects of the Suzuki coupling were examined to determine the ideal reaction conditions (Table 4). While the standard alkaline conditions for the Suzuki coupling include 2.0 M Na_2CO_3, yields of coupled material increased dramatically and reproducibly with the use of cesium fluoride.[70] The coupling could be performed in

Table 4



162 R = CH_3
163 R = Bn

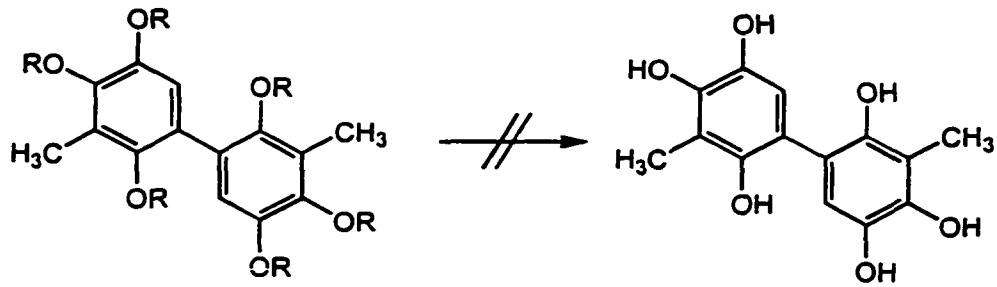
Run	Boronic Acid	Aryl Halide	Conditions	Biaryl (%)
a	-	**142** R = CH_3, X = Br	i	23
b	**146a** R = CH_3	**142** R = CH_3, X = Br	ii	41
c	**146a** R = CH_3	**142** R = CH_3, X = Br	iii	49
d	**146a** R = CH_3	**142** R = CH_3, X = Br	iv	66
e	**146a** R = CH_3	**143** R = CH_3, X = I	v	67
f	**146d** R = Bn	**145** R = Bn, X = I	iv	90
g	**146d** R = Bn	**145** R = Bn, X = I	v	80
h	**146d** R = Bn	**144** R = Bn, X = Br	v	83

Conditions: i) *s*-BuLi, TMEDA, $(CH_3O)_3B$, THF; then $(Ph_3P)_4Pd$, 2 M Na_2CO_3, PhH, **141**, Δ; ii) $(Ph_3P)_4Pd$, 2 M Na_2CO_3, PhH, Δ; iii) $(Ph_3P)_4Pd$, 2 M Na_2CO_3, DME, Δ; iv) $(Ph_3P)_4Pd$, CsF, DME, Δ; v) $(Ph_3P)_4Pd$, CsF, PhH, Δ.

benzene (PhH) or dimethoxyethane (DME) and tetra-kis(triphenylphosphine)palladium, $Pd(Ph_3P)_4$, proved to be a suitable catalyst.

With significant amounts of coupled material available, deprotections of both the hexamethoxy and the hexabenzyloxy series were explored. Simple methyl ethers are known for being robust and difficult to deprotect,[71] however, several methods were attempted. While subjection of biaryl **162** to mild deprotection methods (PhSH, NaH [72]; PhSH, KO-*t*-Bu [73]) gave no new products, the harsher reagent BBr_3[74] (2 equiv., CH_2Cl_2,

-78 °C), removed two of the methyl ethers (Scheme XXIX). By successively increasing the amounts of BBr_3, removal of 4 methyl ethers was possible; however, while excess BBr_3 (> 10 equiv.) apparently removed all of the protecting groups, a failure to isolate the deprotected material was likely due to the instability of the bis-hydroxydihydroquinone product **164** in air.[75] A ^1H NMR analysis of the crude material revealed no identifiable peaks and hence complete decomposition of the oil was presumed.



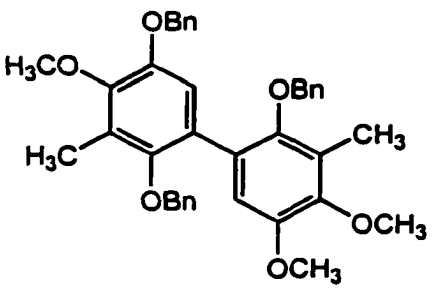
162 R = CH_3
163 R = Bn

164

Scheme XXIX

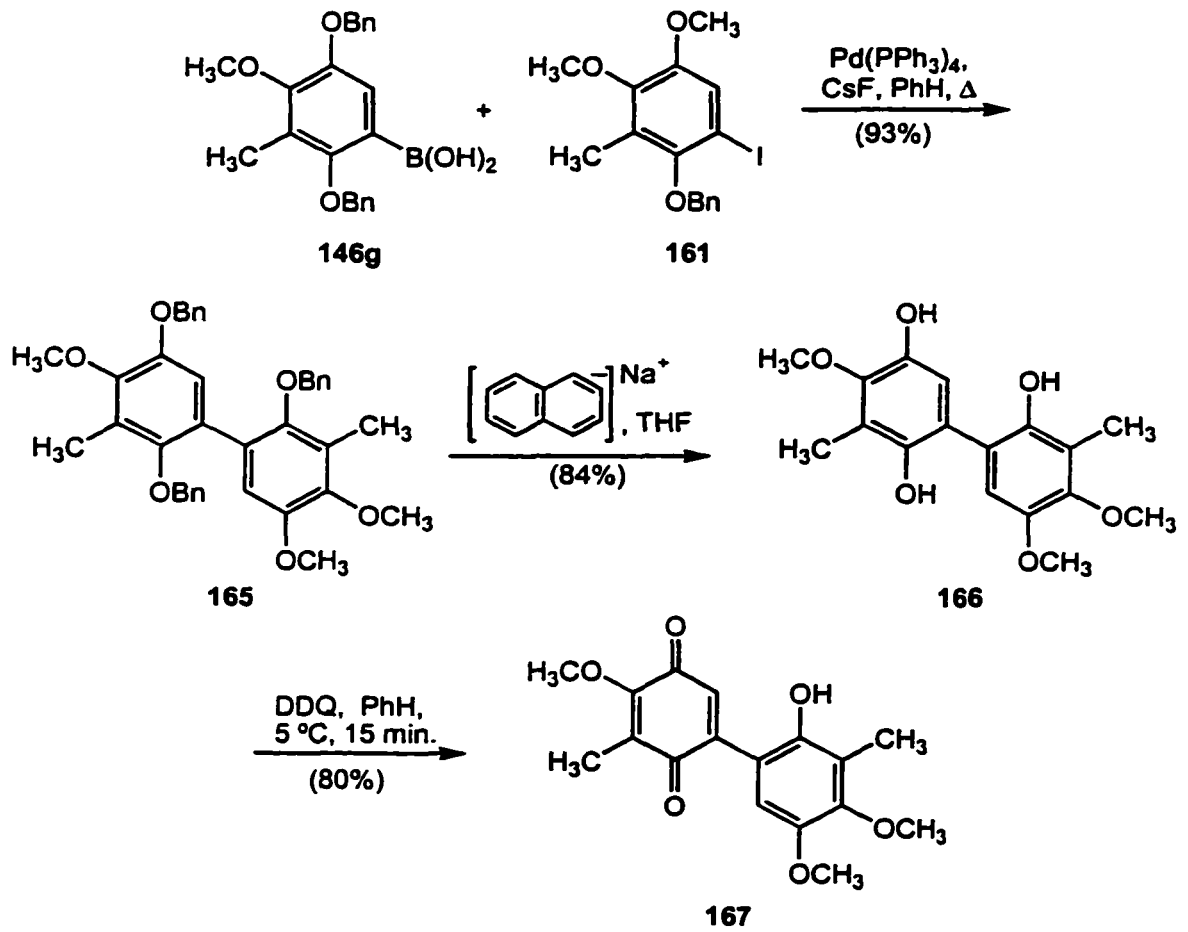
With the thoughts that a benzyl ether might be removed under milder conditions, attention was turned to the benzyloxy protected series. Surprisingly, hydrogenolysis (H_2, Pd/C) of the hexabenzyloxy biaryl **163** could not be achieved even with applied pressure. This may have been due to the congested ring system and the inaccessibility of the catalyst.[76] Fortunately, dissolving metal conditions (Na, NH_3, -78 °C) consumed the starting material, and a crude ^1H NMR analysis showed deprotection of all the phenolic moieties. However, upon isolation TLC detected a variety of compounds. Even though the initial product was exposed to air over a very short period of time, it most likely oxidized to quinones.[75]

Because of these unexpected complications with the protecting groups, a differentially protected biaryl system was prepared that would allow only those positions that were required for the cyclization step to be selectively exposed. The ultimate substrate **165** (Figure 16) would allow for quinone formation and exposure of the requisite phenol. Suzuki coupling of the boronic acid **161** to aryl iodide **146** provided biaryl **165** in high yield (93%)(Scheme XXX).



165

Figure 16

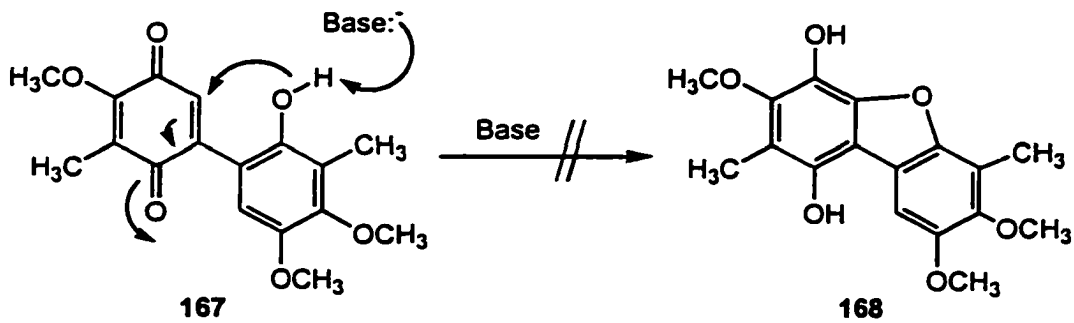


Scheme XXX

The benzyl protecting groups were removed by standard hydrogenolysis (H_2; 10% Pd/C), giving the desired product, triol **166**. However, as with the hexabenzyloxy series, this was not a dependable method to provide the triol. Using decolorizing carbon to remove any impurities remaining from the Suzuki coupling reaction and changing the catalyst repeatedly during the course of the reaction did not allow for reproducible results. The biaryl system **165** does not exist as a planar molecule and has aromatic rings in an orthogonal orientation. This conformation interferes with the phenyl rings interacting with the palladium catalysts and therefore makes deprotection difficult. Alternatively, dissolving metal conditions could be used to provide this triol, but yields

were never greater than 65%. The use of sodium naphthalanide[77] was found to be an easy and efficient way of generating triol **166** in excellent yield (84%) on a routine basis. Subsequent oxidation of the dihydroquinone (DDQ, PhH, 5 °C) provided quinone **167** as a stable, brown solid.

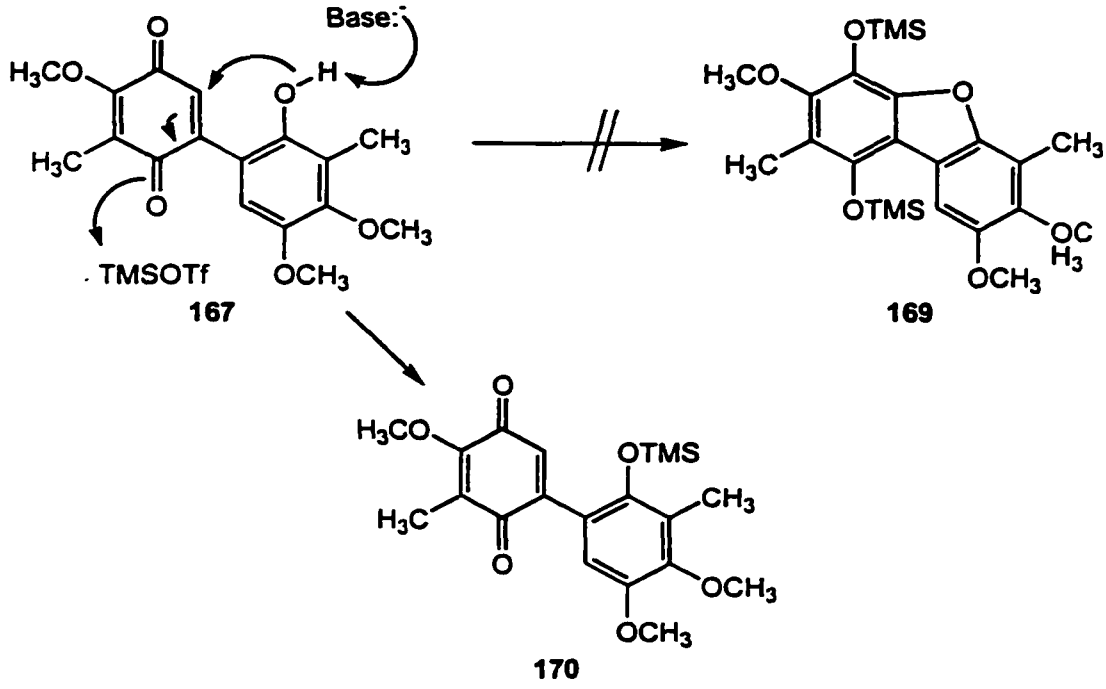
With the hydroxyquinone **167** available in sufficient quantity, the formation of the core furan ring was investigated. The cyclization was attempted using various bases (Et_3N, KH, NaH, or KO*t*-Bu), but the starting material was returned unchanged (Scheme XXXI).



167 **168**

Scheme XXXI

The possibility that the addition was reversible was also investigated by attempting to trap the 1,4-addition product by treatment with Et_3N/TMSOTf to form the bis-silylated hydroquinone **169**, but these conditions converted the phenol to the silyl ether **170** (Scheme XXXII). With these experiments, we presumed that no intramolecular-1,4-addition was actually occurring under basic conditions because of the nonplanarity of the molecule.[78] According to Baldwin's rules of ring closure,[79]



Scheme XXXII

this is a 5-*endo*-trig cyclization that is kinetically disfavored. With the biaryl system in an orthogonal conformation, the amount of energy associated with overcoming the strain involved with aligning the HOMO of the phenoxide anion with the LUMO of the quinone to form the central furan ring may have been too high (Figure 17).

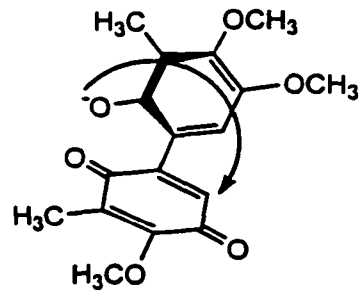
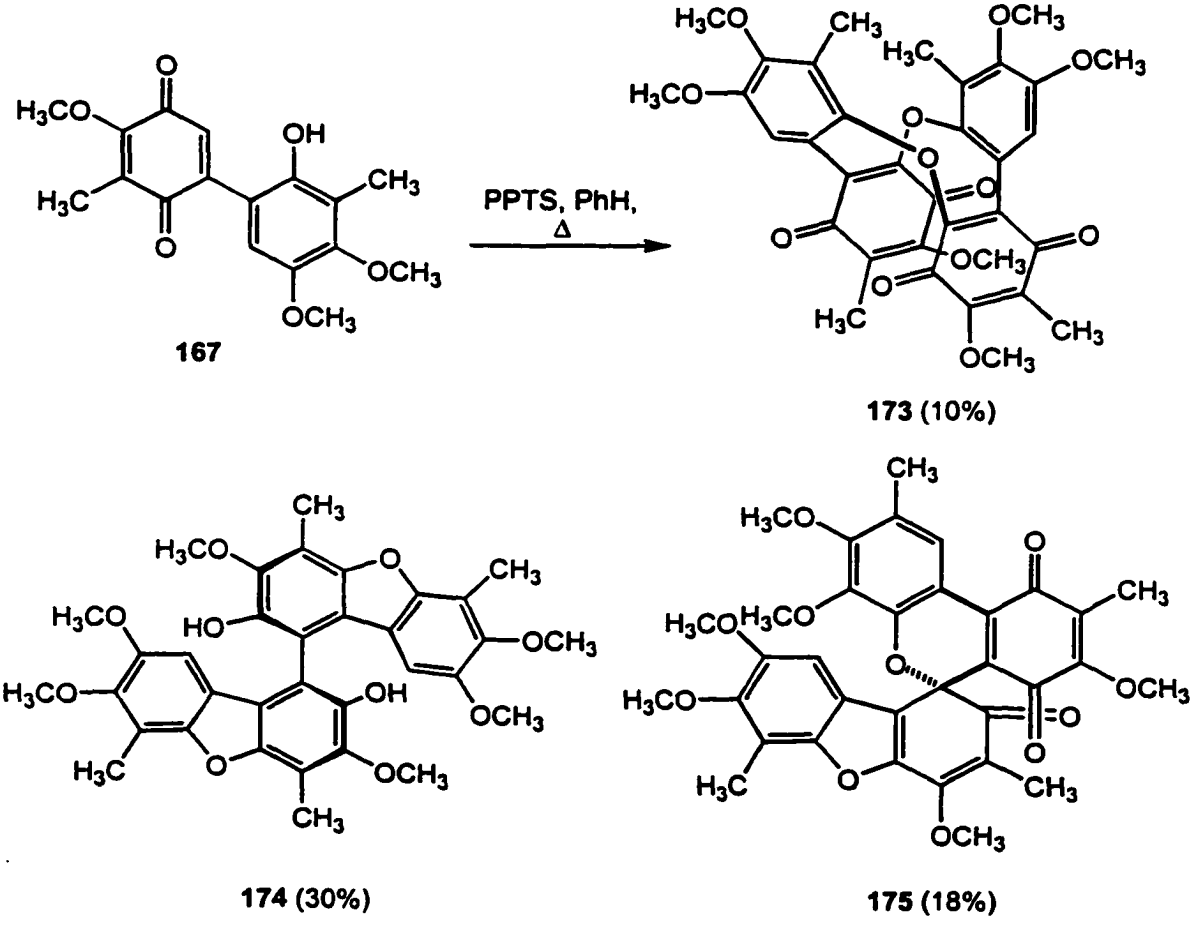


Figure 17

Refluxing the hydroxyquinone **167** in the presence of a catalytic amount of pyridinium *para*-toluene sulfonate (PPTS, PhH) provided several new products: **173** (10%), **174** (30%), **175** (18%) and a fourth fraction **176** (7%) that was a mixture of products for which the structures could not be determined (Scheme XXXIII). For compound **173**, the IR displayed absorptions at 1667 and 1656 cm^{-1} which are characteristic of a quinone functionality. Since the ^{1}H NMR spectrum had only 6 signals and the ^{13}C NMR had 17 signals, the material initially appeared to be monomeric, but the high resolution mass spectral data (*m/e* = 632) indicated that the molecule was actually dimeric; the mass was



167

173 (10%)

174 (30%)

175 (18%)

Scheme XXXIII

twice the starting material (mass of **167** = 318) less the mass of 4 hydrogen atoms suggestive of an oxidative dimerization process. The standard spectroscopic techniques provided little evidence for the structural assignment of any of the products from the acid catalyzed cyclization; therefore, the more sophisticated long range NMR techniques HMQC (Heteronuclear Multiple Quantum Coherence), NOE (Nuclear Overhauser Effect), HMBC (Heteronuclear Multiple Bond Connectivity), NOESY (Nuclear Overhauser and Exchange Spectroscopy), and COSY (Correlated Spectroscopy) were utilized (Table 5).[80]

HMBC and HMQC are highly sensitive techniques that are closely related, but provide different data. In the HMQC analysis, determinations of one bond connectivities between a proton and the carbon to which it is attached can be made, whereas HMBC studies determine long range couplings between a proton and a carbon 2 or 3 bonds away. The NOESY spectrum shows an enhancement of a signal when a nearby resonance is irradiated and then transfers that excitation energy through space to nearby protons. The resultant enhancements in signals indicate that protons are close to each other in space. With COSY, through-bond couplings between protons can be determined. From the information gained from these analyses, the assignments of individual ring systems can be made.

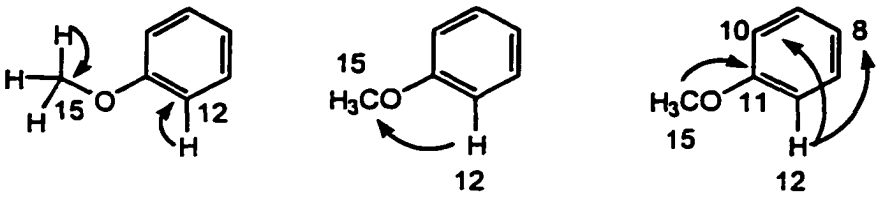
For dimer **173**, the resonance at δ 100.6 ppm was assigned to C-12, and from the HMQC data the proton at δ 7.36 ppm was determined to be attached to it (Figure 18, **A**). The resonance at δ 56.1 ppm was assigned to C-15 and connectivity to the methoxyl protons resonating at δ 3.93 ppm was established by HMQC. The C-12 and C-15

Table 5

Spectral Data for Compound 173

C #	HMQC ^{13}C	HMQC ^{1}H	NOE (H/H)	HMBC (50 ms)	HMBC (100 ms)
1	184.2	-	-	-	-
2	129.5	-	-	-	-
3	155.8	-	-	-	-
4	172.6	-	-	-	-
5	150.5	-	-	-	-
6	122.6	-	-	-	-
7	117.2	-	-	-	-
8	151.5	-	-	-	-
9	117.4	-	-	-	-
10	149.6	-	-	-	-
11	152.9	-	-	-	-
12	100.6	7.36	12/15	10; 8	10; 8: 6 or 7
13	9.04	2.45	13/14	8; 9; 10	8; 9; 10
14	60.9	3.85	14/13	10	10
15	56.1	3.93	15/12	11	11
16	8.84	2.03	16/17	1; 2; 3	1; 2; 3
17	61.3	4.06	17/16	3	3

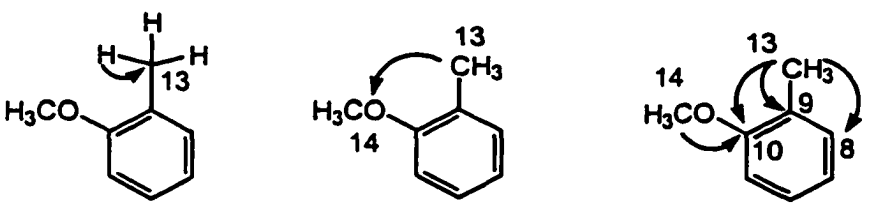
carbons were placed within the same ring system based on the NOESY study which indicated a proximal relationship between the C-12 proton and the protons corresponding to the C-15 methoxyl group (Figure 18, **B**). The HMBC analysis was instrumental in establishing that the C-15 methoxyl group was attached to the aromatic ring at carbon C-11 (δ 152.9 ppm). Additional long-range couplings between the C-12 proton and the carbons C-8 (δ 151.5 ppm) and C-10 (δ 149.6 ppm) were observed at 50 and 100ms (Figure 18, **C**). Using this information, parts of an aromatic ring for **173** could be established (Figure 18).



HMQC A | NOESY B | HMBC C

Figure 18

The ^{13}C NMR showed 2 resonances that were easily identified as the aryl methyls at δ 9.04 (C-13) and δ 8.84 (C-16) (Figure 19). From the HMQC study, connectivity between the C-13 methyl group and the protons resonating at δ 2.45 was established (Figure 19). From the NOE data, proximity between the C-13 methyl and the methoxyl group resonating at δ 3.85 was determined. The HMBC data showed that long range C-H coupling existed between the C-13 methyl group and the carbons resonating at δ 151.5, δ 117.4, and δ 149.6 (C-8, C-9, and C-10, respectively). The HMBC data established the methoxy group (C-14) as attached to the aromatic carbon resonating at δ 149.6 (C-10) and allowed for the following partial ring assignment (Figure 19).



HMQC A | NOE B | HMBC C

Figure 19

The C-16 methyl carbon was determined to have the protons resonating at δ 2.03 attached to it by an HMQC study and showed proximity to the methoxy group at δ 4.06 (C-17) by NOE analysis (Figure 20). Its long-range coupling as determined by HMBC was to a new set of aromatic carbons: δ 184.2, δ 129.5, and δ 155.8 (C-1, C-2, and C-3, respectively) (Figure 20). The C-1 resonance is a carbonyl and is part of the second ring system of this molecule. Also, by HMBC, the C-17 methoxy group displayed long-range coupling to the aromatic carbon resonating at δ 155.8 to allow for the partial assignment in Figure 20.

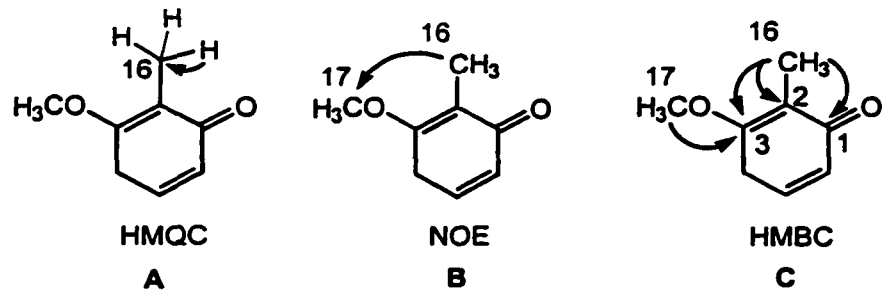


Figure 20

By combining these partial structures, a structure for this compound was determined to be that shown in Figure 21. Although several of the connectivities for the carbons corresponding to C-4, C-5, C-6 and C-7 could not be established, some deductions could be made based on known chemical shifts. The C-4 carbon resonating at δ 172.6 was far downfield and was assumed to be the other carbonyl of the 1,4-benzoquinone system in Figure 20. However, it was impossible to accurately assign the carbons that were involved in the biaryl linkage because none of the 2-D NMR techniques showed coupling between the rings. Based on the available information, we are confident that this is the structure of the product **173**.

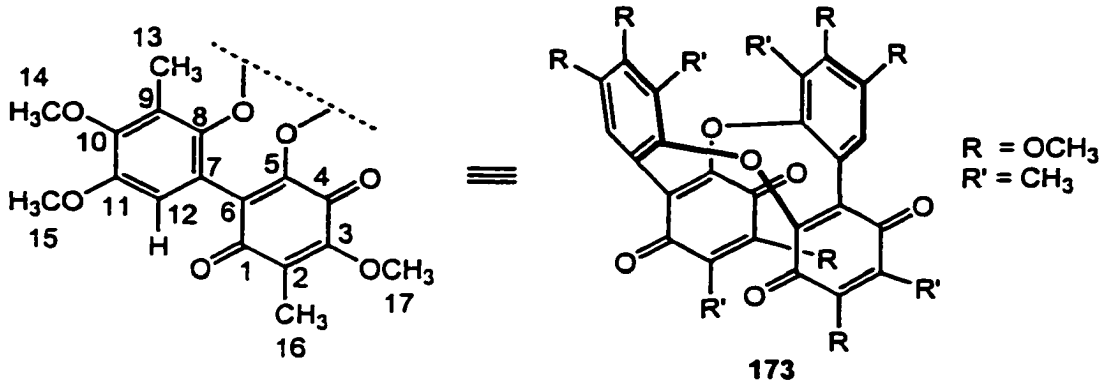


Figure 21

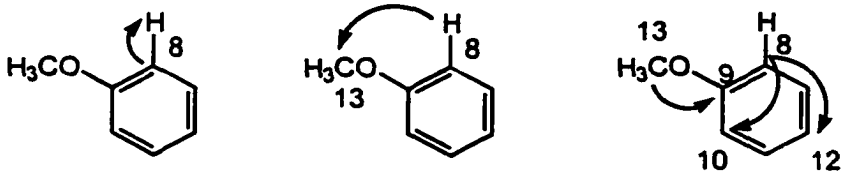
Compound **174** had very unique spectral data (Table 6). In addition to a mass spectrum that indicated another dimeric structure (*m/e* = 602), there is a broad stretch centered at 3434 cm^{-1} in the IR spectrum that is characteristic of a phenol and this assignment was supported by an exchangeable proton in the ^{1}H NMR. The molecule was assumed to be symmetrical in nature since neither the ^{1}H and ^{13}C NMR spectra for **174** displayed a doubling in number of peaks.

From the 2-D NMR data, the carbon resonance at δ 101.1 was assigned to C-8 and the proton attached to it resonated at δ 6.14 as determined in the HMQC analysis (Table 6). The protons on C-8 were proximal to the methoxy group resonating at δ 3.40 (C-13) as observed in the NOE spectrum and the HMBC analysis established that this methoxy group was attached to the aryl carbon resonance of δ 149.2 (C-9). From the HMBC analysis for C-8, the carbons resonating at δ 146.9 (C-10) and δ150.7 (C-12) were also found in this ring. Considering this information, another partial structure was determined (Figure 22).

Table 6

Spectral Data for Compound **174**

C #	HMQC ^{13}C	HMQC ^{1}H	COSY	NOE (H/H)	HMBC (50 ms)
1	149.8	-	-	-	-
2	115.6	-	-	-	-
3	144.7	-	-	-	-
4	143.0	-	-	-	-
5	110.4	-	-	-	-
6	119.1	-	-	-	-
7	118.7	-	-	-	-
8	101.0	6.14	-	8/13	10;12
9	149.2	-	-	-	-
10	146.9	-	-	-	-
11	115.2	-	-	-	-
12	150.7	-	-	-	-
13	55.7	3.40	13/8	13/8	9
14	60.7	3.73	-	14/15	10
15	9.13	2.45	15/8	15/14	10; 11; 12
16	9.70	2.64	-	16/17	2; 3; 1
17	61.5	3.96	-	17/16	3



HMQC A NOE B HMBC C

Figure 22

The aryl methyl group resonating at δ 9.13 (C-15) was essential in determining another ring system (Figure 23). This carbon had attachment to the methyl protons at δ 2.45 established by HMQC. The NOE analysis for this methyl group revealed proximity to the methoxy resonating at δ 60.7 (C-14) and HMBC analysis determined that this

methoxy group was attached to the aromatic ring at the carbon resonating at δ 146.9. Additional couplings between the C-15 carbon and the carbons resonating at δ 146.9, δ 115.2 and δ 150.7 (C-10, C-11 and C-12, respectively) were ascertained from the HMBC analysis. The COSY spectrum displayed long-range coupling to the C-8 aromatic proton and allowed for the assignment of the ring in Figure 23.

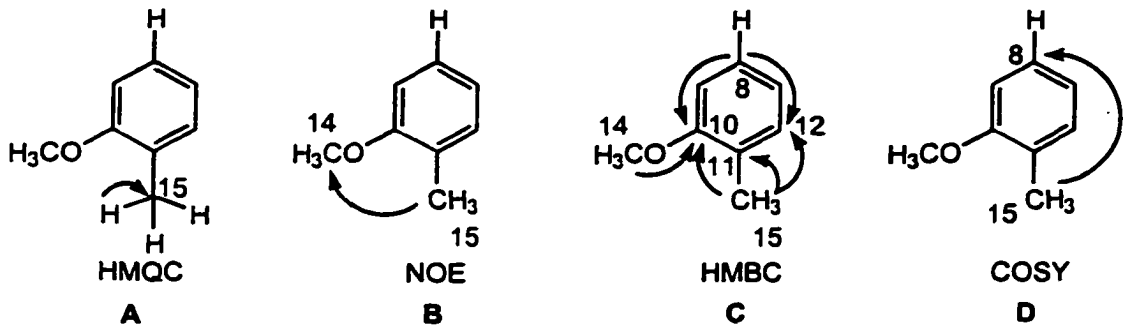


Figure 23

The other methyl group also provided insight into a partial ring structure. The methyl group resonating at δ 9.70 (C-16) was attached to the protons resonating at δ 2.64 (HMQC) and displayed long range coupling to the carbons resonating at δ 149.8, δ 115.6 and δ 144.7 (C-1, C-2, and C-3 respectively) in the HMBC study. Additional information from the NOE data established that the C-16 aryl methyl group was proximal to the methoxy group resonating at δ 3.96 (C-17) and from the HMBC, this methoxy group was found to be connected to the ring by the carbon resonating at 144.7 (C-3) (Figure 24).

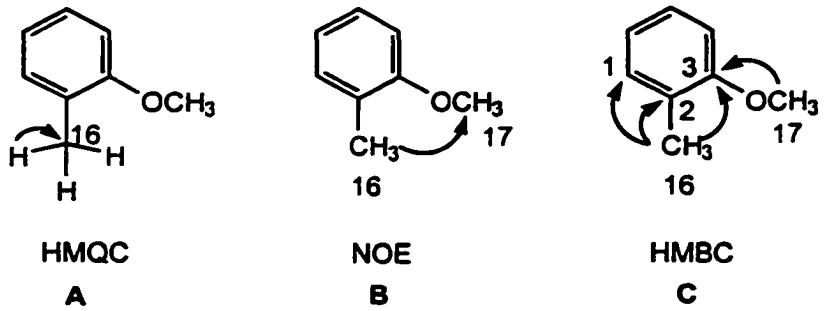


Figure 24

From this analysis, the two rings in Figures 22 and 23 were determined to belong to the same ring system and that in Figure 24 to an independent system (Figure 25). The aromatic carbons resonating at δ 143.0, 110.4, 119.1 and 118.7 (C-4, C-5, C-6 and C-7, respectively) were unidentifiable in the structure by the 2-D NMR studies. However, since the C-4 carbon resonated downfield (δ 143.0), as with the other aromatic carbons that were attached to oxygen, it was assigned to be the carbon attached to the phenol. Since the resonances for carbons C-5, C-6 and C-7 are relatively close to each other, their assignments are interchangeable.

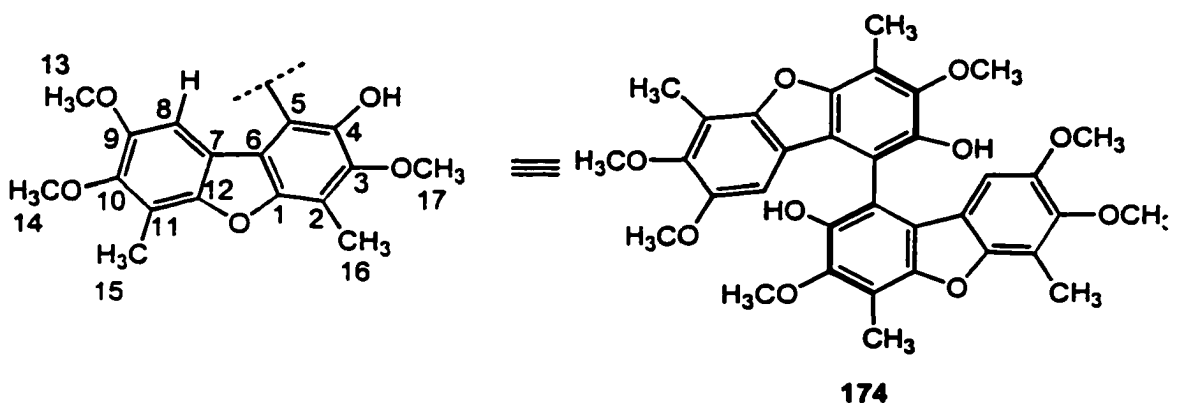


Figure 25

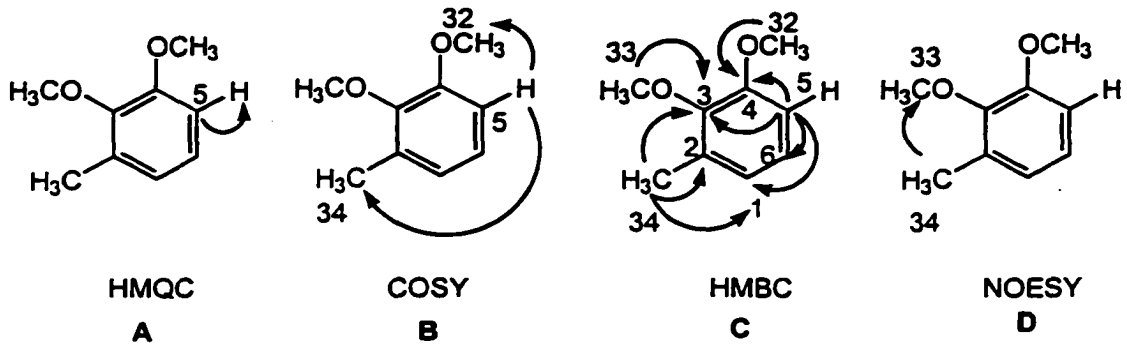
The characterization of the structure for compound **175** was more difficult. The IR spectrum displayed stretches at 1681 and 1649 cm^{-1} that were indicative of the presence of a carbonyl functionality. The high resolution mass spectral data with *m/e* = 616 verified and the complex NMR data were compelling evidence that the compound was another dimer and not a mixture. The 2-D NMR data were very important to solving the structure for this compound (Table 7). A total of three carbonyls were present in the ^{13}C NMR data and, since the material was not symmetrical, the analysis would now involve four aromatic ring systems.

The aromatic carbon resonating at δ 109.0 (C-5) was attached to the proton resonating at δ 8.05 (HMQC) (Figure 26). This aromatic proton showed coupling in the H/H COSY to the methoxy group resonating at δ 3.88 (C-32) and long range coupling to the aryl methyl protons resonating at δ 1.88 (C-34). The C-5 aromatic proton showed couplings to the aromatic carbons resonating at δ 147.4, δ 151.9, δ 148.3, and δ 132.8 (C-1, C-3, C-4 and C-6, respectively) in the HMBC analysis (Figure 26). Also by HMBC, the C-32 methoxy group was determined to be attached to the ring at the carbon resonating at δ 148.3. Since the C-34 aryl methyl group was associated with this system, that information was combined with the present data. From the NOESY, the C-34 methyl group showed proximity to the methoxy group resonating at δ 3.77 (C-33). The HMBC data displayed couplings between the same C-34 methyl group and the carbons resonating at δ 147.4, δ 121.8, and δ 151.9 (C-1, C-2, and C-3 respectively) and a coupling between the C-33 methoxy group and the carbon resonating at 151.9 (C-3) to allow for the structural assignment in Figure 26.

Table 7

Spectral Data for Compound **175**

C #	HMQC ^{13}C	HMQC ^{1}H	COSY (C/H)	NOESY (H/H)	HMBC HC (50 ms)	HMBC CH (100 ms)
1	147.4	-	-	-	-	-
2	121.8	-	-	-	-	-
3	151.9	-	-	-	-	-
4	148.3	-	-	-	-	-
5	109.0	8.05	5/32 5/34	5/20	1; 3	4; 6
6	132.8	-	-	-	-	-
7	120.4	-	-	-	-	-
8	187.5	-	-	-	-	-
9	128.6	-	-	-	-	-
10	154.8	-	-	-	-	-
11	180.3	-	-	-	-	-
12	132.7	-	-	-	-	-
13	76.3	-	-	-	-	-
14	192.4	-	-	-	-	-
15	146.7	-	-	-	-	-
16	130.4	-	-	-	-	-
17	149.7	-	-	-	-	-
18	111.9	-	-	-	-	-
19	116.0	-	-	-	-	-
20	98.9	5.74	20/25 20/27	20/5	22; 24	21; 22 19 or 18
21	150.5	-	-	-	-	-
22	145.7	-	-	-	-	-
23	116.1	-	-	-	-	-
24	149.7	-	-	-	-	-
25	9.00	2.36	25/20	25/26	22; 23; 24	22; 23; 24
26	60.8	3.71	-	26/25	22	22
27	55.6	3.41	27/20	-	21	21
28	10.3	2.38	-	28/29	15; 16; 17	15; 16; 17
29	60.2	3.91	-	29/28	15	15
30	61.0	3.87	-	30/31	10	10
31	9.00	1.95	-	31/30	8; 9; 10	8; 9; 10
32	56.0	3.88	32/5	-	4	4
33	60.6	3.77	-	33/34	3	3
34	8.98	1.88	34/5	34/33	1; 2; 3	1; 2; 3



HMQC A | COSY B | HMBC C | NOESY D

Figure 26

An HMQC analysis of the aromatic carbon resonating at δ 98.9 (C-20) in the ^{13}C NMR revealed connectivity to the aromatic proton resonating at δ 5.74 while the H/H COSY showed couplings to the aromatic methyl group [δ 2.36 (C-25)] and to the methoxy group [δ 3.41 (C-27)] (Figure 27). HMBC analysis of C-20 established that carbons resonating at δ 150.5, δ 145.7, δ 149.7 and either of the carbons at δ 111.9 or 116.0 (C-21, C-22, C-24 and either C-18 or 19) were present in this ring system. Through the HMBC study, the C-27 methoxy group was determined to be attached to the ring at the aromatic carbon resonating at δ 150.5 (C-21) and the C-26 methoxy group at the carbon resonating at δ 145.7 (C-22). The C-25 aromatic methyl displayed proximity to the methoxy group resonating at δ 3.71 (C-26) in the NOESY analysis and couplings to the aromatic carbon resonating at δ 116.1 (C-23) and C-22 and C-24 in the HMBC study.

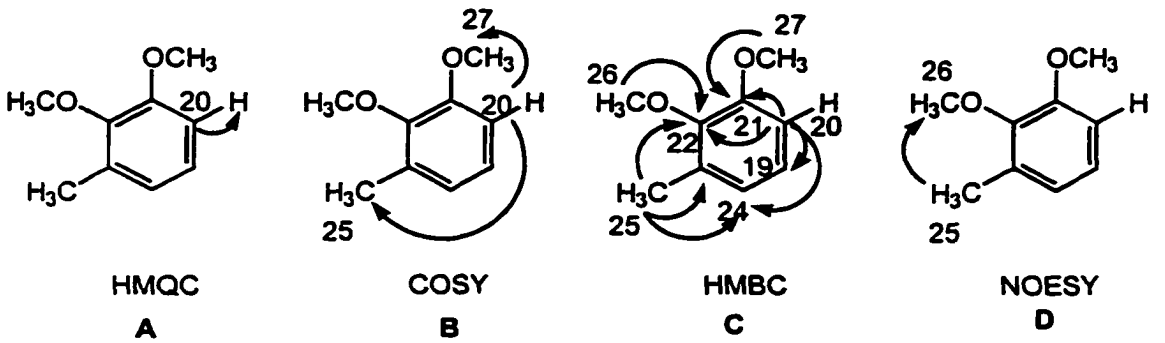


Figure 27

The remaining two aryl methyl groups resonating at δ 10.3 and δ 9.00 (C-28 and C-31) in the ^{13}C NMR spectrum had not displayed involvement in the previous systems and were useful in completing the structural analysis. The C-31 aryl methyl carbon was determined to have the methyl protons at δ 1.95 attached to it by HMQC analysis and to be proximal to the methoxy group resonating at δ 3.91 (C-30) by NOESY (Figure 28). The HMBC data for C-31 displayed couplings to the carbons resonating at δ 187.5, δ 128.6 and δ 154.8 (C-8, C-9 and C-10, respectively). The HMBC analysis of the C-30 methoxyl group established that it was attached to the aromatic carbon resonating at δ 154.8 (C-10).

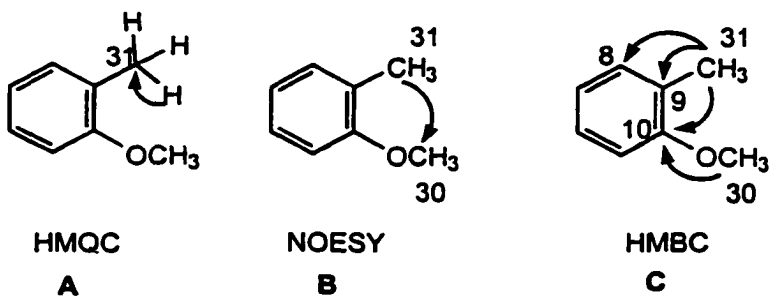
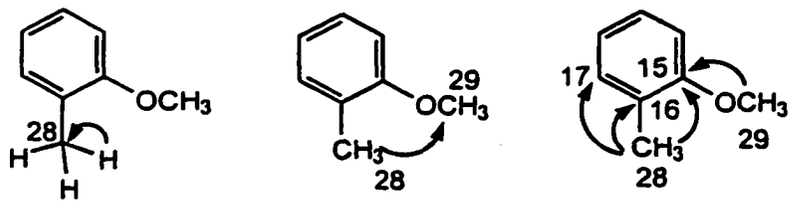


Figure 28

The C-28 methyl carbon was determined to be attached to the methyl protons resonating at δ 2.38 (HMQC analysis) and showed proximity to the methoxy group resonating at δ 3.91 (C-29) in the NOESY study (Figure 29). The coupling between the C-28 methyl carbon and the carbons resonating at δ 146.7, δ 130.4, and δ 149.7 (C-15, C-16, and C-17, respectively) found in the HMBC analysis was useful in determining the other carbons present in the ring system. The C-29 methoxyl group displayed coupling to the carbon resonating at δ 146.7 (C-15) in the HMBC to allow for the final ring assignment shown in Figure 29.

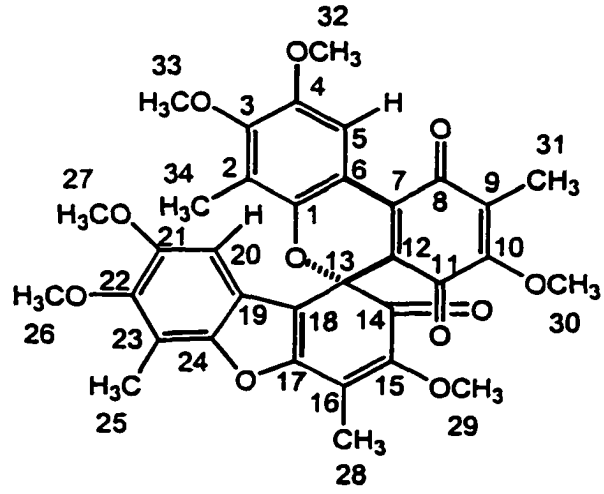


HMQC A NOESY B HMBC C

Figure 29

After taking into account all of the coupling data, six carbons in the ^{13}C NMR spectrum remained unaccounted for in the structures; C-7, C-11, C-12, C-13, C-14 and C-18. The C-11 (δ 180.3) and C-14 (δ 192.4) carbons were downfield and were characterized as carbonyls and, since no coupling was displayed for either of them, their assignments in the proposed structure are interchangeable. Since all of the methoxyl carbons were accounted for in the partial structures, the upfield C-13 carbon resonance (δ 76.3) suggested that destruction of the aromatic ring system had occurred. The C-7 carbon (δ 120.4) was believed to be adjacent to one of the carbonyls and involved in the

biaryl linkage. This assignment corresponds to the approximate peak position for the biaryl linkage of compound **173** (C-6, δ 122.6). The C-12 and C-18 peaks resonating at δ 132.7 and δ 111.9 were identified as aromatic carbons and their specific identification in the overall structure shown in Figure 30 is interchangeable.



175

Figure 30

After repeated column chromatography, it was possible to obtain one of the three compounds of the mixture **176**, and HRMS data revealed that the material was dimeric with *m/e* = 632, another dimerization product. However, complete determination of the structure remained elusive (Table 8). The partial structure for the compounds was difficult to determine because of the poor resolution of the aryl methyl carbons which were an important starting point for the earlier solutions. The NOESY and the COSY spectra also did not display readily identifiable cross-peaks to allow for the identification of coupling between the methyl and methoxyl groups and the aryl protons.

Table 8

Spectral Data for Compound **176**

C #	HMQC ^{13}C	HMQC ^{1}H	COSY (C/H)	NOESY (H/H)	HMBC (50 ms)
1	8.79	1.87*	1 or 2/13	-	16; 23; 25
2	8.88	1.94*	1or 2/8 or 5	1 or 2/8 or 5	20; 30; 33
3	8.89	2.13*	3/8	-	18; 24; 28
4	11.3	1.61	-	5 or 8/14	11; 22; 29; 34
5	55.9	3.75	5 or 8/14	6/13	26
6	56.1	3.60	6/13	-	27
7	58.3	4.37	-	5 or 8/14	29
8	60.5	3.73	5 or 8/14	-	25
9	60.7	3.86	-	-	28
10	61.4	4.01	-	-	30
11	64.4	-	-	-	-
12	83.1	-	-	-	-
13	106.2	5.99	-	-	23; 25
14	108.3	7.15	-	-	24; 28
15	113.0	-	-	-	-
16	116.3	-	-	-	-
17	118.8	-	-	-	-
18	122.7	-	-	-	-
19	128.2	-	-	-	-
20	129.0	-	-	-	-
21	135.6	-	-	-	-
22	139.8	-	-	-	-
23	146.6	-	-	-	-
24	147.3	-	-	-	-
25	148.73	-	-	-	-
26	149.0	-	-	-	-
27	149.3	-	-	-	-
28	152.6	-	-	-	-
29	154.7	-	-	-	-
30	154.9	-	-	-	-
31	172.2	-	-	-	-
32	180.1	-	-	-	-
33	186.2	-	-	-	-
34	192.7	-	-	-	-

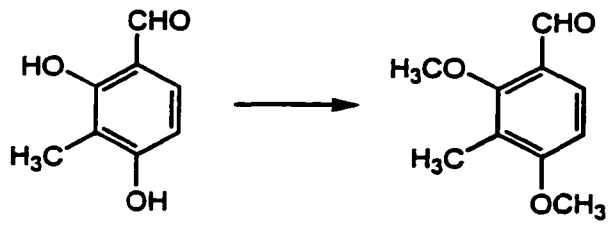
Experimental Section

General

^{1}H NMR spectra were measured at 360 or 300 MHz and ^{13}C spectra were measured at 90 or 75 MHz on either a Bruker AMX 360 or a General Electric GN 300 respectively. All samples were prepared in deuterochloroform and referenced to an internal standard, tetramethylsilane. Infrared spectra were recorded on a Mattson FT-IR and samples were prepared as thin films on NaCl plates. Melting points were taken on a Mel-Temp apparatus and are uncorrected.

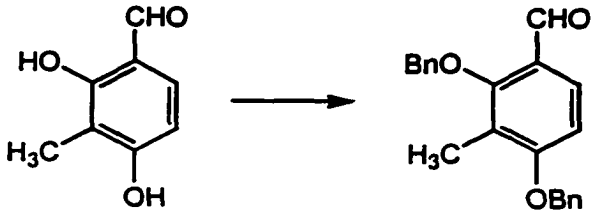
All reactions were run in glassware that had been flame dried and kept under a nitrogen atmosphere unless otherwise noted. Tetrahydrofuran (THF) and diethyl ether (Et_2O) were distilled from sodium/benzophenone ketyl prior to use. Benzene (PhH), toluene ($PhCH_3$) and methylene chloride (CH_2Cl_2) were distilled from calcium hydride. The tri-O-methoxy borate and the tri-O-isopropyl borate were dried over sodium metal overnight and then distilled prior to use. The *m*-CPBA and the NBS were purified prior to use.[81]

Chemicals were purchased from Aldrich Chemical Company (SIGMA), Fisher and VWR and were used as received unless otherwise noted. Alkyl lithiums were titrated on a monthly basis to establish accurate titers. All chromatography solvents were distillled from glass prior to use and silica gel 60 from EM Science was used for flash chromatography. Thin layer chromatography plates were precoated with $60F_{254}$ (0.25 mm or 0.50 mm thickness) and were purchased through EM Science. For purification via preparatory TLC, compounds were extracted from the silica gel utilizing ethyl acetate and all isolated samples were placed under vacuum (0.5 atm) at room temperature until constant weight was obtained.



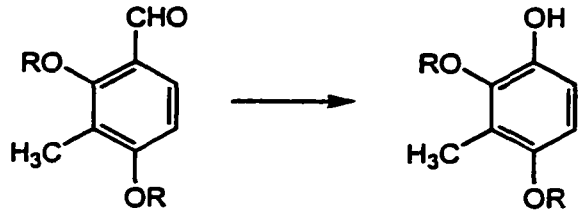
135 **136**

2,4-Dimethoxy-3-methylbenzaldehyde (136). To a solution of 1.95 g (12.8 mmol) of **134** in acetone (64 mL) was added 3.55 g (28.2 mmol) of dimethylsulfate and 4.45 g (32.0 mmol) of K_2CO_3. The mixture was refluxed 12 h, and after cooling to room temperature, the solvent was removed by rotary evaporation. The resulting mixture was diluted with EtOAc (50 mL) and washed with H_2O (50 mL) and then with sat. (saturated) brine (2 x 50 mL). The organic layer was dried over Na_2SO_4, filtered and concentrated *in vacuo* to leave a colorless oil that was purified by flash chromatography (400 g SiO_2; 20% EtOAc/Hexanes) to provide 2.30 g (99%) of dimethoxybenzaldehyde **17** as a white solid: mp 150-151 °C, lit. val. 152-153 °C; R_f = 0.44 in 30% EtOAc/Hexanes; ^{1}H NMR δ 10.23 (s, 1H), 7.74 (d, J = 8.8 Hz, 1H), 6.75 (d, J = 8.8 Hz, 1H), 3.90 (s, 3H), 3.86 (s, 3H), 2.16 (s, 3H) ppm.



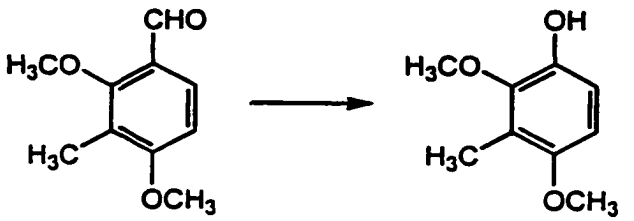
135 137

2,4-Dibenzyloxy-3-methylbenzaldehyde (137). To a solution of 0.375 g (2.46 mmol) of **16** in acetone (12.5 mL) was added 0.936 g (7.39 mmol) of benzyl chloride, 9.10 mg (0.0246 mmol) of tetra-*n*-butyl ammonium iodide (*n*-Bu_4NI), and 0.749 g (5.42 mmol) potassium carbonate (K_2CO_3). The mixture was refluxed for 12 h and then cooled to room temperature. After removing the solvent by rotary evaporation, the residue was dissolved in EtOAc (20 mL) and washed with H_2O (2 x 20 mL) and sat. brine (2 x 20 mL). The organic phase was dried over Na_2SO_4, filtered and concentrated to a yellow oil that was purified by flash chromatography (50 g SiO_2; 20% EtOAc/Hexanes) to provide 0.611 g (75%) of **136** as a white solid: mp 67-69 °C; R_f = 0.42 in 30% EtOAc/Hexanes; IR (thin film) υ 3030, 2926, 1678, 1455, 1277, 1100 cm^{-1}; ^1H NMR δ 10.16 (s, 1H), 7.46-7.37 (m, 10H), 7.74 (d, J = 8.7 Hz, 1H), 6.83 (d, J = 8.7 Hz, 1H), 5.16 (s, 2H), 4.96 (s, 2H), 2.27 (s, 3H) ppm; ^{13}C NMR δ 188.8, 162.9, 161.0, 136.2, 128.5, 128.4, 128.1, 128.0, 127.7, 123.3, 120.7, 107.9, 77.7, 70.3, 9.1 ppm; Anal. Calcd for $C_{22}H_{20}O_3$: C, 79.50; H, 6.06. Found: C, 79.19; H, 5.89.



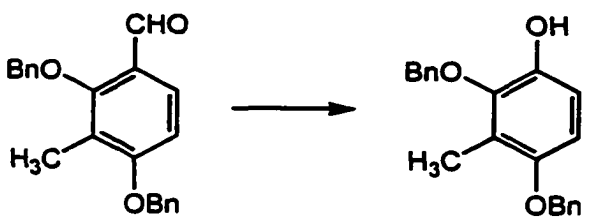
General Procedure I (Baeyer-Villiger Oxidation/Saponification of Benzaldehydes):

A 0.2 M solution of the benzaldehyde in CH_2Cl_2 was cooled to 0 °C and *m*-CPBA (1.1 eq.) was added with stirring. The mixture was slowly warmed to room temperature over 12 h and then was washed with sat. $NaHCO_3$ (3x), water and sat. brine. The organic layer was dried over Na_2SO_4, filtered and concentrated to a yellow oil that was used without further purification. The crude residue was dissolved in CH_3OH (0.2 M solution) and a 25% wt/wt solution of sodium methoxide (1.2 eq.) was added. The mixture was heated for 3 h and then the solvent removed *in vacuo* to provide a dark brown oil that was dissolved in Et_2O and washed with saturated aqueous NH_4Cl solution. The aqueous layer was washed with additional Et_2O (2x) and the combined organic layers were washed with sat. brine. The organic extract was dried over Na_2SO_4, filtered and concentrated *in vacuo* to provide a yellow oil that was purified by flash chromatography.



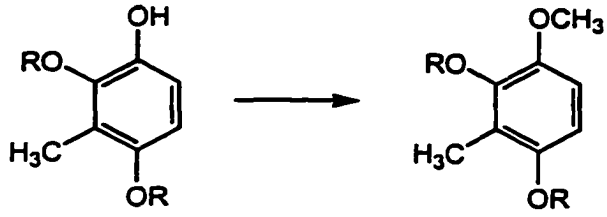
136 138

2,4-Dimethoxy-3-methylphenol (138). Colorless oil; R_f = 0.35 in 30% EtOAc/Hexanes; IR (neat) υ 3544-3530, 3015, 1489 cm^{-1}; ^1H NMR δ 6.75 (d, J = 10.8 Hz, 1H), 6.53 (d, J = 10.8 Hz, 1H), 5.63 (bs, 1H), 3.75 (s, 6H), 2.17 (s, 3H) ppm; ^{13}C NMR δ 151.9, 146.0, 142.9, 120.0, 111.8, 106.8, 60.6, 56.0, 9.1 ppm; Anal. Calcd for $C_9H_{12}O_3$: C, 64.27; H, 7.19. Found: C, 64.62; H, 7.20.



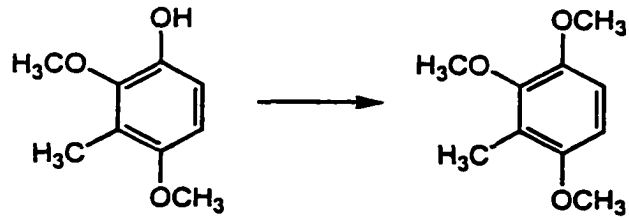
137 139

2,4-Dibenzyloxy-3-methylphenol (139). Colorless oil; R_f = 0.42 in 30% EtOAc/Hexanes; IR (neat) υ 3535-3525, 3032, 2924, 1490, 1264, 1228 cm^{-1}; ^1H NMR δ 7.41-7.30 (m, 10H), 6.63 (AB quartet, J_{AB} = 10.6 Hz, Δν = 45.7 Hz, 2H), 5.27 (s, 1H), 4.95 (s, 2H), 4.82 (s, 2H), 2.24 (s, 3H) ppm; ^{13}C NMR δ 150.9, 144.9, 143.3, 137.5, 136.8, 128.7, 128.6, 128.4, 128.3, 128.1, 127.6, 127.1, 120.8, 111.8, 108.7, 75.4, 70.8, 9.9 ppm; Anal. Calcd for $C_{21}H_{20}O_3$: C, 78.73; H, 6.29. Found: C, 78.34; H, 6.37.



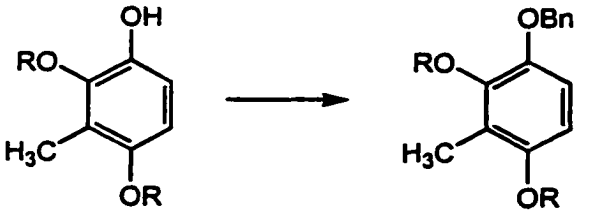
General Procedure II (Aryl Methyl Ether Formation):

A 0.2 M solution of sodium hydride (1.5 eq.) in dry THF was cooled to 0 °C and a 0.1 M solution of phenol in THF was slowly added dropwise via an addition funnel. Once the evolution of H_2 had ceased, dimethyl sulfate (3 eq.) was added. The solution was warmed to room temperature (12 h) and then the solvent was removed *in vacuo*. The mixture was dissolved in EtOAc and washed twice with H_2O and sat. brine. The organic layer was dried over Na_2SO_4, filtered and concentrated *in vacuo* to leave a clear liquid which was purified by flash chromatography.



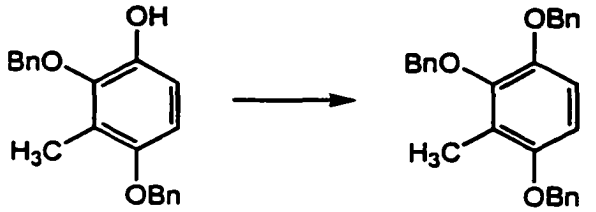
138 **140**

2,3,6-Trimethoxytoluene (140). Yellow oil; R_f = 0.49 in 30% EtOAc/Hexanes; IR (thin film) ν 2997, 2834, 1491, 1260, 1118 cm^{-1}; ^1H NMR δ 6.61 (AB quartet, J_{AB} = 10.8 Hz, Δν = 56.6 Hz, 2H), 3.80 (s, 3H), 3.78 (s, 3H), 3.76 (s, 3H), 2.15 (s, 3H) ppm; ^{13}C NMR δ 152.6, 148.1, 121.2, 109.6, 105.3, 60.3, 65.3, 55.9, 8.9 ppm.



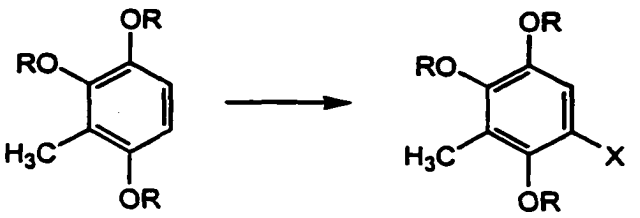
General Procedure III (Aryl Benzyl Ether Formation):

To a 0.2 M solution of phenol in acetone was added benzyl chloride (1.5 eq.), K_2CO_3 (1.2 eq.), and *n*-Bu_4NI (0.1 eq.). The mixture was refluxed 12 h and then cooled to room temperature. After concentrating the mixture *in vacuo*, the residue was dissolved in EtOAc and washed twice with H_2O and brine. The organic phase was dried over Na_2SO_4, filtered and concentrated to a yellow oil that was purified by flash chromatography.



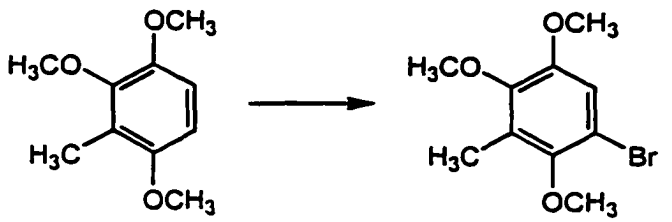
139 **141**

2,3,6-Tribenzyloxytoluene (141). White solid; mp 107-108 °C; R_f = 0.50 in 30% EtOAc/Hexanes; IR (thin film) υ 3064, 2927, 2867, 1498, 1262, 1109 cm^{-1}; ^1H NMR δ 7.47-7.32 (m, 15H), 6.71 (AB quartet, J_{AB} = 8.9 Hz, Δν = 63.1 Hz, 2H), 5.10 (s, 2H), 5.04 (s, 2H), 5.03 (s, 2H), 2.22 (s, 3H) ppm; ^{13}C NMR δ 151.9, 147.7, 146.5, 137.7, 137.5, 137.4, 128.4, 128.3, 127.9, 127.8, 127.7, 127.5, 127.1, 122.2, 111.9, 107.1, 74.7, 71.6, 70.6, 9.9 ppm.



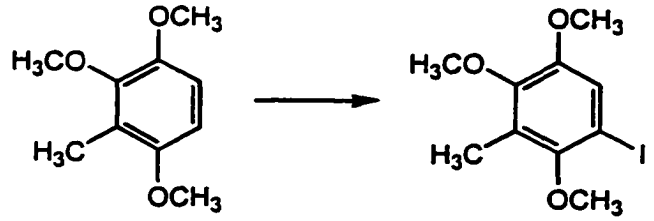
General Procedure IV (Aryl Bromide/Iodide Formation):

To a 0.2 M solution of protected toluene derivative in THF was added either *N*-iodo (NIS) or *N*-bromosuccinimide (NBS) (1.3 eq.) and a drop of H_2SO_4. The mixture was stirred for 12 h in the dark. The solvent was removed *in vacuo* and the residue dissolved in EtOAc and washed with saturated $NaHCO_3$, H_2O, and sat. brine. The organics were dried over Na_2SO_4, filtered and concentrated to a brown oil that was purified by flash chromatography.



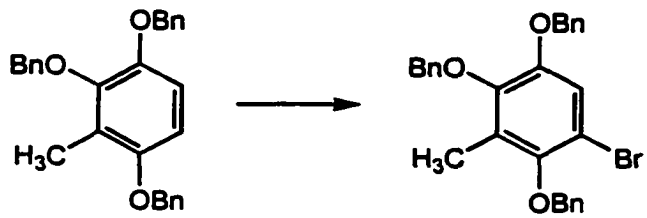
140 **142**

5-Bromo-2,3,6-trimethoxytoluene (142). Yellow oil; R_f = 0.60 in 30% EtOAc/Hexanes; IR (thin film) ν 3002, 2937, 1483, 1230, 1089 cm^{-1}; ^1H NMR δ 6.92 (s, 1H), 3.81 (s, 3H), 3.77 (s, 3H), 3.74 (s, 3H), 2.24 (s, 3H) ppm; ^{13}C NMR δ 149.8, 149.5, 147.4, 127.1, 113.8, 110.6, 60.3, 60.2, 56.1, 10.1 ppm.



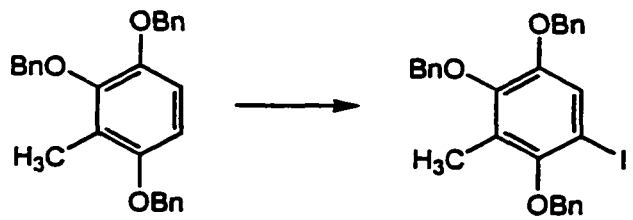
140 143

5-Iodo-2,3,6-trimethoxytoluene (143). Yellow oil; R_f = 0.55 in 30% EtOAc/Hexanes; IR (thin film) ν 2997, 2868, 1480, 1234, 1090 cm^{-1}; ^1H NMR δ 7.11 (s, 1H), 3.80 (s, 3H), 3.77 (s, 3H), 3.70 (s, 3H), 2.25 (s, 3H) ppm; ^{13}C NMR δ 152.4, 150.0, 148.4, 126.1, 119.3, 83.7, 60.3, 60.1, 56.1, 10.4 ppm.



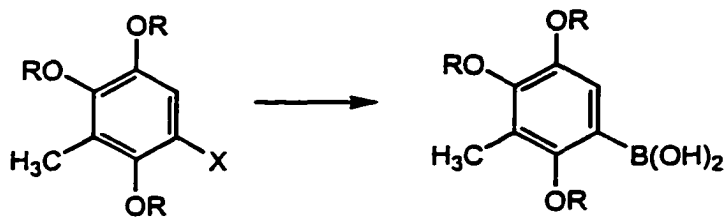
141 144

5-Bromo-2,3,6-tribenzyloxytoluene (144). White solid; mp XX-XX °C; R_f = 0.73 in 30% EtOAc/Hexanes; IR (thin film) ν 3033, 2931, 1499, 1232, 1073 cm^{-1}; ^1H NMR δ 7.52-7.30 (m, 15H), 7.09 (s, 1H), 5.09 (s, 2H), 4.98 (s, 2H), 4.86 (s, 2H), 2.15 (s, 3H) ppm; ^{13}C NMR δ 149.1, 137.3, 137.0, 136.5, 128.5, 128.4, 128.3, 128.2, 128.1, 128.0, 127.9, 127.5, 115.8, 111.1, 74.7, 74.6, 71.4, 10.8 ppm; Anal. Calcd for $C_{28}H_{25}BrO_3$: C, 68.72; H, 5.15. Found: C, 68.64; H, 5.12.



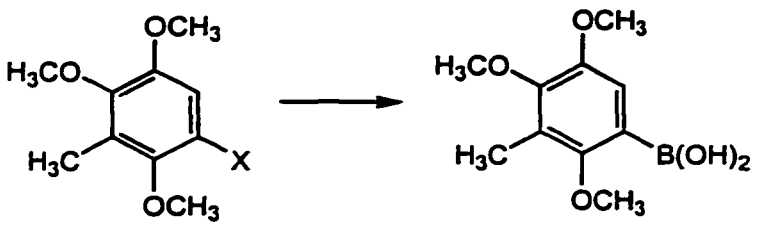
141 **145**

5-Iodo-2,3,6-tribenzyloxytoluene (145). White solid; mp 81-82 °C; R_f = 0.60 in 30% EtOAc/Hexanes; IR (thin film) ν 3003, 1498, 1227, 1217 cm^{-1}; ^1H NMR δ 7.61-7.35 (m, 16H), 5.08 (s, 2H), 4.99 (s, 2H), 4.82 (s, 2H), 2.18 (s, 3H) ppm; ^{13}C NMR δ 151.4, 149.4, 147.9, 137.4, 136.9, 136.6, 128.4, 128.2, 128.1, 127.6, 127.3, 121.5, 84.3, 74.7, 71.6, 11.1 ppm; Anal. Calcd for $C_{28}H_{25}IO_3$: C, 62.70; H, 4.70. Found: C, 62.68; H, 4.77.



General Procedure V (Boronic Acid Preparation):

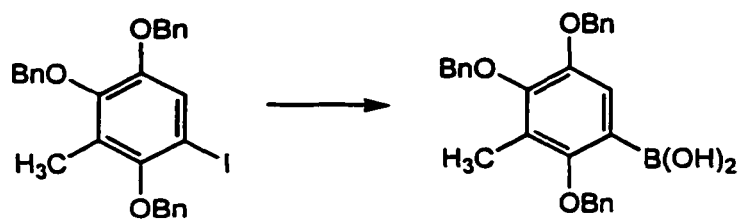
A 0.2 M solution of aryl iodide or bromide in THF was cooled to $^{-}$78 °C and *s*-BuLi (2.1 eq.) was slowly added dropwise. After stirring 45 min., tri-O-isopropyl borate was added and the flask was warmed to room temperature. The solids were dissolved by the addition of 10% HCl solution (3 drops) and stirring for 5 more minutes. The mixture was transferred to a separatory funnel using Et_2O and washed twice with 10% HCl solution. The aqueous layer was washed with Et_2O (2x) and the combined organic layers were dried over Na_2SO_4, filtered and concentrated by rotary evaporation. Final purification by flash column chromatography provided a white solid.



142 X = Br
143 X = I

146a

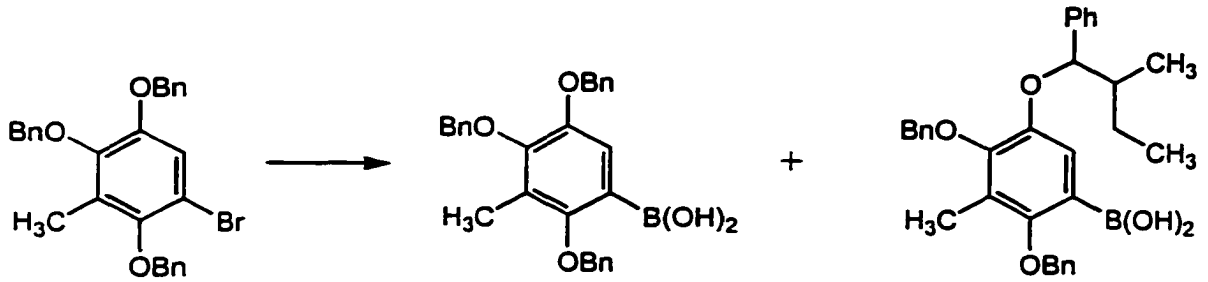
3-Methyl-2,4,5-trimethoxybenzene boronic acid (**146a**). White solid; mp 95-97 °C; R_f = 0.29 in 30% EtOAc/Hexanes; IR (thin film) ν 3462-3387, 2958, 1410, 1350, 1090 cm^{-1}; ^1H NMR δ 7.20 (s, 1H), 6.05 (bs, 2H), 3.88 (s, 3H), 3.84 (s, 3H), 3.75 (s, 3H), 2.22 (s, 3H) ppm; ^{13}C NMR δ 158.9, 151.0, 149.4, 124.6, 115.5, 115.4, 62.0, 60.2, 55.9, 9.46 ppm.



145

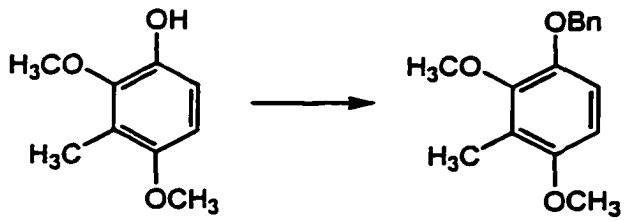
146d

2,4,5-Tribenzyloxy-3-methylbenzene boronic acid (**146d**). White solid; mp 105-106 °C; R_f = 0.35 in 30% EtOAc/Hexanes; IR (thin film) ν 3405, 3032, 2929, 1453, 1069, 973 cm^{-1}; ^1H NMR δ 7.48-7.30 (m, 16H), 6.01 (s, 2H), 5.15 (s, 2H), 5.06 (s, 2H), 4.77 (s, 2H), 2.20 (s, 3H) ppm; ^{13}C NMR δ 157.6, 150.2, 148.8, 137.5, 137.0, 136.0, 128.9, 128.3, 128.0, 127.9, 126.6, 125.5, 117.4, 77.1, 74.5, 71.0, 10.2 ppm.



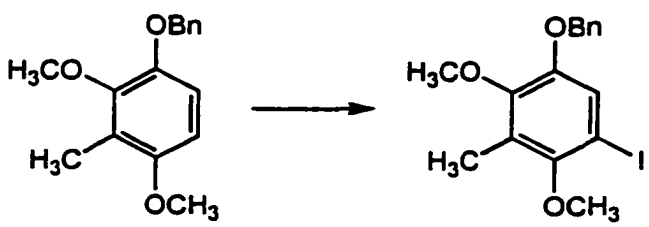
5-[2'-methyl-1'-phenyl]butanoxy-2,4-dibenzyloxy-3-methylbenzene boronic acid (147c).

Yellow oil; R_f = 0.44 in 30% EtOAc/Hexanes; IR (thin film) ν 3471-3417, 3064, 2963, 2875, 1588, 1496, 1065 cm^{-1}; ^1H NMR (major diastereomer) δ 7.65-7.35 (m, 16H), 6.02 (s, 2H), 5.29 (AB quartet, J_{AB} = 10.9 Hz, Δν = 10.6 Hz, 2H), 5.21 (d, J = 6.6 Hz, 1H), 4.83 (s, 2H), 2.30 (s, 3H), 2.29-2.12 (m, 1H), 1.95-1.89 (m, 1H), 1.47 - 1.37 (m, 1H), 1.07 (t, J = 7.4 Hz, 3H), 1.10 (d, J = 6.8 Hz, 3H) ppm; ^{13}C NMR δ 157.0, 150.1, 148.2, 140.1, 137.8, 136.1, 128.7, 128.6, 128.4, 128.3, 128.1, 128.0, 127.4, 127.1, 126.8, 125.2, 118.1, 84.2, 74.5, 41.4, 25.2, 15.2, 11.5, 10.2 ppm.



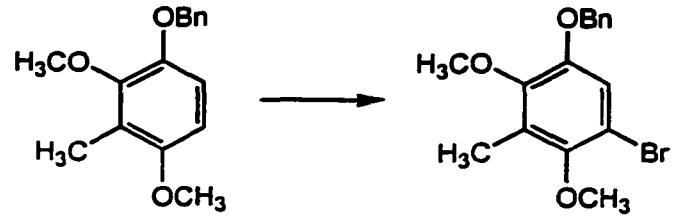
138 **151**

3-Benzyloxy-2,6-dimethoxytoluene (151). Prepared using General Procedure III, white solid; mp 50-51 °C; R_f = 0.56 in 30% EtOAc/Hexanes; IR (thin film) ν 2995, 2833, 1488, 1260, 1089, 1028 cm^{-1}; ^1H NMR δ 7.45-7.30 (m, 5H), 6.61 (AB quartet, J_{AB} = 8.9 Hz, Δν 88.2 Hz, 2H), 5.05 (s, 2H), 3.84 (s, 3H), 3.76 (s, 3H), 2.16 (s, 3H) ppm; ^{13}C NMR δ 152.8, 146.1, 137.6, 128.3, 127.6, 127.2, 121.1, 112.1, 112.0, 111.9, 71.5, 60.3, 55.7, 8.9 ppm; Anal. Calcd for $C_{16}H_{18}O_3$: C, 74.40; H, 7.02. Found: C, 74.61; H, 7.32



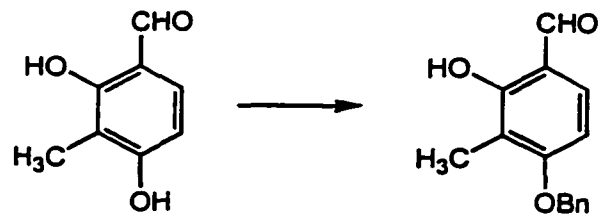
151 **152**

3-Benzyloxy-2,6-dimethoxy-5-iodotoluene (152). Prepared using General Procedure IV, yellow oil; R_f = 0.57 in 30% EtOAc/Hexanes; IR (thin film) ν 3088, 3032, 2932, 1497, 1259, 1092, 1001 cm^{-1}; ^1H NMR δ 7.45-7.37 (m, 5H), 7.21 (s, 1H), 5.04 (s, 2H), 3.83 (s, 3H), 3.72 (s, 3H), 2.27 (s, 3H) ppm; ^{13}C NMR δ 152.7, 149.2, 149.0, 136.6, 128.5, 128.0, 127.3, 126.4, 121.1, 83.7, 71.2, 60.4, 10.5 ppm.



151 153

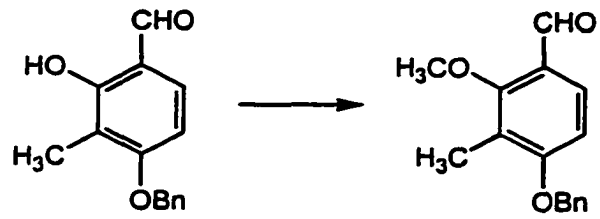
3-Benzyloxy-5-bromo-2,6-dimethoxytoluene (153). Prepared as in General Procedure IV, Yellow solid; mp 77-78 °C; R_f = 0.61 in 30% EtOAc/Hexanes; IR (thin film) ν 2934, 1478, 1236, 1097, 1070 cm^{-1}; ^1H NMR δ 7.43-7.35 (m, 5H), 7.00 (s, 1H), 5.02 (s, 2H), 3.81 (s, 3H), 3.74 (s, 3H), 2.25 (s, 3H) ppm; ^{13}C NMR δ 151.0, 149.5, 147.3, 139.8, 128.6, 128.0, 127.3, 115.6, 71.3, 60.4, 10.1 ppm.



135 154

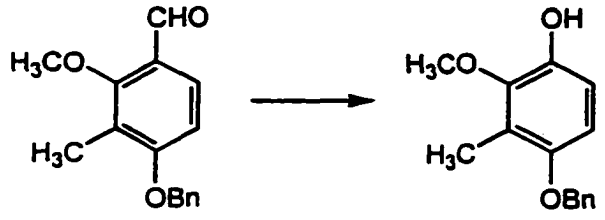
4-Benzyloxy-2-hydroxy-3-methylbenzaldehyde (154). To a flask containing 7.75 g (51.0 mmol) of aldehyde in 250 ml acetone was added 2.93 g (25.5 mmol) of BnCl, 3.52 g (25.5 mmol) of K_2CO_3, and 1.88 g (5.10 mmol) of *n*-Bu_4NI. The contents were stirred and heated at reflux for 12 h. After cooling to room temperature, the solvent was removed by rotary evaporation and the remaining mixture dissolved in 200 mL H_2O and transferred to a separatory funnel. The aqueous layer was extracted with Et_2O (3 x 200

mL) and the combined organics dried over Na_2SO_4, filtered, and concentrated to a yellow oil. Final purification by column chromatography (750 g SiO_2, 10% EtOAc/ Hexanes) gave 8.00 g (81%) of **153** as a white solid: mp 44-45 °C; R_f = 0.49 in 30% EtOAc/Hexanes; IR (thin film) ν 3089, 2926, 1625, 1501, 1285, 1106 cm^{-1}; ^1H NMR δ 11.52 (s, 1H), 9.49 (s, 1H), 7.34-7.22 (m, 5H), 7.13 (d, J = 8.6 Hz, 1H), 6.43 (d, J = 8.6 Hz, 1H), 4.96 (s, 2H), 2.11 (s, 3H) ppm; ^{13}C NMR δ 194.3, 162.9, 160.6, 135.9, 132.8, 132.7, 128.2, 127.7, 126.6, 115.1, 113.1, 103.6, 69.7, 7.2 ppm.



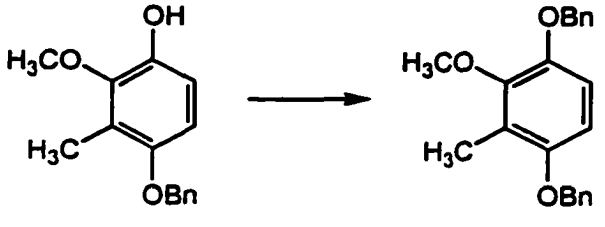
154 **155**

4-Benzyloxy-2-methoxy-3-methylbenzaldehyde (155). Prepared using General Procedure II, white solid; mp 76-77 °C; R_f = 0.33 in 25% Et_2O/Hexanes; IR (thin film) ν 3006, 2951, 1685, 1598, 1290, 1111 cm^{-1}; ^1H NMR δ 10.22 (s, 1H), 7.70 (d, J = 8.7 Hz, 1H), 7.43-7.32 (m, 5H), 6.77 (d, J = 8.7 Hz, 1H), 5.11 (s, 2H), 3.84 (s, 3H), 2.21 (s, 3H) ppm; ^{13}C NMR δ 188.9, 162.9, 162.5, 136.1, 128.5, 128.0, 127.7, 127.0, 122.8, 120.3, 107.6, 70.1, 62.9, 8.6 ppm.



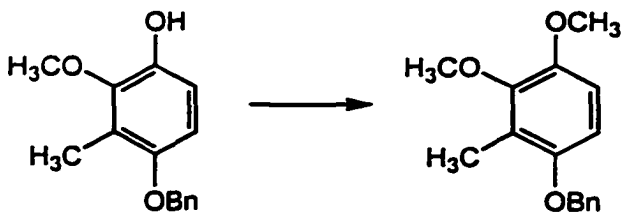
155 156

4-Benzyloxy-2-methoxy-3-methylphenol (156). Prepared using General Procedure I, yellow oil; R_f = 0.32 in 30% EtOAc/Hexanes; IR (thin film) ν 3507-3410, 2998, 1488, 1238, 1190 cm^{-1}; ^1H NMR δ 7.45 - 7.30 (m, 5H), 6.68 (AB quartet, J_{AB} = 8.8 Hz, Δν = 46.8 Hz, 2H), 5.28 (s, 1H), 5.01 (s, 2H), 3.79 (s, 3H), 2.23 (s, 3H) ppm; ^{13}C NMR δ 151.0, 146.1, 143.3, 137.6, 128.4, 127.7, 127.2, 120.7, 111.8, 108.8, 71.1, 60.8, 9.5 ppm.



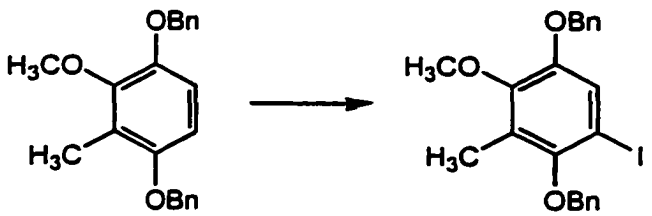
156 157

3,6-Dibenzyloxy-2-methoxytoluene (157). Prepared using General Procedure III, colorless oil; R_f = 0.56 in 30% EtOAc/Hexanes; IR (thin film) ν 3038, 2957, 1487, 1266 cm^{-1}; ^1H NMR δ 7.45-7.15 (m, 10H), 6.62 (AB quartet, J_{AB} = 8.9 Hz, Δν = 59.5 Hz, 2H), 5.03 (s, 2H), 4.97 (s, 2H), 3.85 (s, 3H), 2.25 (s, 3H) ppm; ^{13}C NMR δ 152.1, 149.0, 146.4, 137.6, 128.4, 127.7, 127.6, 127.3, 127.1, 121.8, 112.2, 107.0, 71.6, 70.7, 60.4, 9.2 ppm; Anal. Calcd for $C_{22}H_{22}O_3$: C, 79.02; H, 6.63. Found: C, 78.76; H, 6.60.



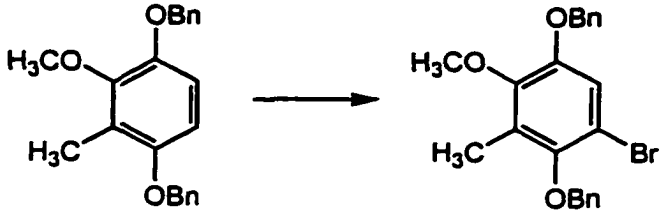
156 158

6-Benzyloxy-2,3-dimethoxytoluene (158). Prepared using General Procedure II, white solid; mp 56-57 °C; R_f = 0.58 in 30% EtOAc/Hexanes; IR (thin film) ν 3063, 2995, 1590, 1488, 1267, 1083 cm^{-1}; ^1H NMR δ 7.48-7.34 (m, 5H), 6.63 (AB quartet, J_{AB} = 8.9 Hz, Δν 25.0 Hz, 2H), 5.04 (s, 2H), 3.85 (s, 3H), 3.83 (s, 3H), 2.28 (s, 3H) ppm; ^{13}C NMR δ 151.4, 148.1, 147.3, 137.5, 128.3, 127.5, 127.0, 121.6, 109.3, 109.1, 106.9, 106.8, 70.5, 60.1, 56.0, 9.1 ppm; Anal. Calcd for $C_{16}H_{18}O_3$: C, 74.40; H, 7.02. Found: C, 74.30; H, 7.04.



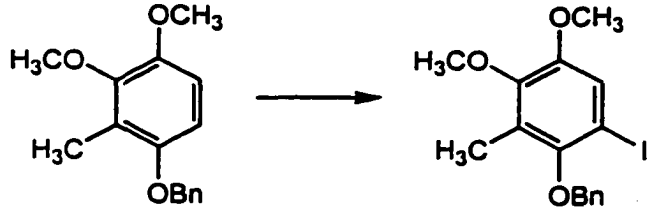
157 159

3,6-Dibenzyloxy-5-iodo-2-methoxytoluene (159). Prepared using General Procedure IV, yellow oil; R_f = 0.56 in 30% EtOAc/Hexanes; IR (thin film) 3063, 3031, 2932, 1497, 1259, 1092 cm^{-1}; ^1H NMR δ 7.56-7.32 (m, 11H), 5.03 (s, 2H), 4.82 (s, 2H), 3.82 (s, 3H), 2.26 (s, 3H) ppm; ^{13}C NMR δ 151.2, 149.3, 148.9, 136.8, 136.6, 128.5, 128.4, 128.2, 128.0, 127.3, 126.8, 121.1, 84.2, 74.6, 71.1, 60.3, 10.7 ppm.



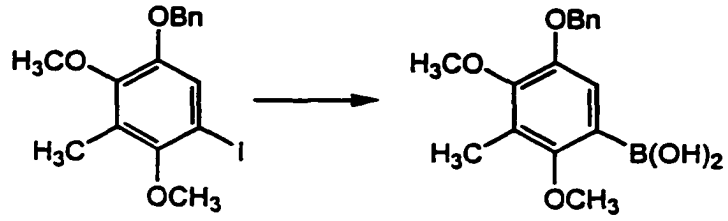
157 160

5-Bromo-3,6-dibenzyloxy-2-methoxytoluene (160). Prepared using General Procedure IV, yellow solid; mp 79-80 °C; R_f = 0.56 in 30% EtOAc/Hexanes; IR (thin film) 3031, 2932, 1477, 1233, 1089 cm^{-1}; ^1H NMR δ 7.53-7.33 (m, 10H), 7.04 (s, 1H), 5.06 (s, 2H), 4.87 (s, 2H), 3.82 (s, 3H), 2.23 (s, 3H) ppm; ^{13}C NMR δ 148.9, 148.5, 148.0, 137.0, 136.6, 128.5, 128.4, 128.1, 128.0, 127.6, 127.3, 115.9, 110.9, 74.6, 71.3, 60.2, 10.3 ppm; Anal. Calcd for $C_{22}H_{21}BrO_3$: C, 63.93; H, 5.12. Found: C, 63.97; H, 5.39.



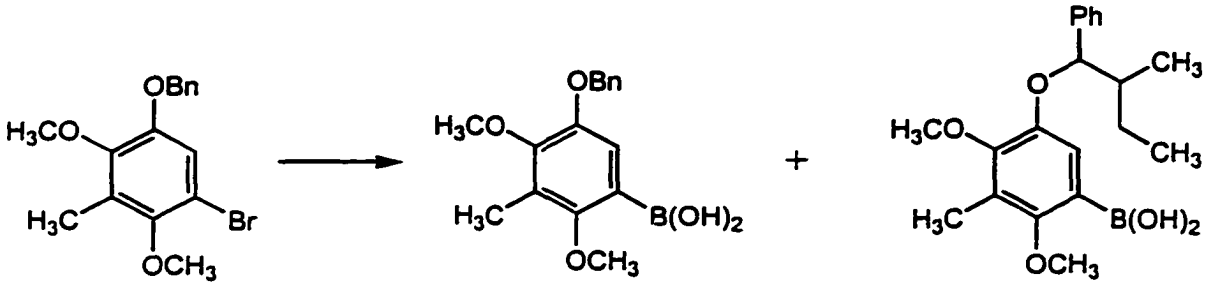
158 161

6-Benzyloxy-5-iodo-2,3-dimethoxytoluene (161). Prepared using General Procedure IV, yellow oil; R_f = 0.63 in 30% EtOAc/Hexanes; IR (thin film) ν 2997, 1586, 1496, 1261, 1175, 1001 cm^{-1}; ^1H NMR δ 7.55-7.31 (m, 5H), 7.13 (s, 1H), 4.80 (s, 2H), 3.76 (s, 6H), 2.24 (s, 3H) ppm; ^{13}C NMR δ 150.6, 149.9, 148.1, 136.6, 128.2, 127.9, 126.4, 119.0, 118.9, 84.2, 74.4, 60.0, 55.8, 10.5 ppm; Anal. Calcd for $C_{16}H_{17}IO_3$: C, 50.01; H, 4.46. Found: C, 50.21; H, 4.51.



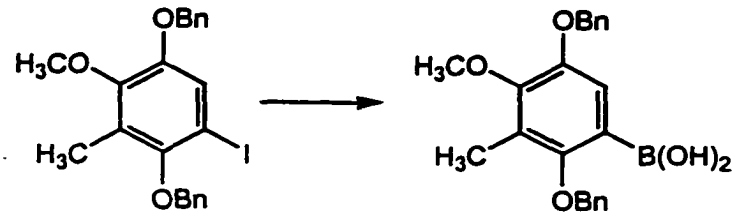
152 **146e**

5-Benzyloxy-2,4-dimethoxy-3-methylbenzene boronic acid **(146e).** Prepared using General Procedure V, colorless oil; R_f = 0.20 in 30% EtOAc/Hexanes; IR (thin film) ν 3522-3302, 3088, 2962, 1484, 1224, 1068, 1003 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.47-7.28 (m, 6H), 5.88 (s, 2H), 5.11 (s, 2H), 3.88 (s, 3H), 3.75 (s, 3H), 2.22 (s, 3H) ppm; ^{13}C NMR ($CDCl_3$) δ 159.2, 151.5, 148.6, 137.1, 128.5, 127.9, 127.4, 124.8, 117.4, 117.3, 70.8, 62.0, 60.3, 9.5 ppm.



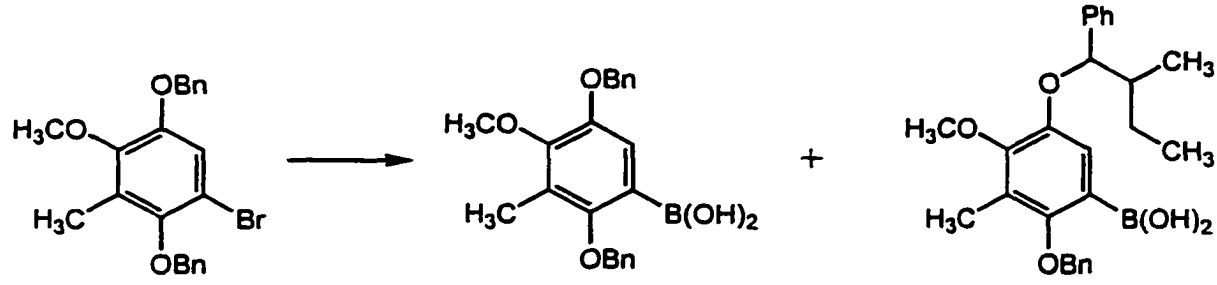
153 **146f** **147f**

5-[2'-methyl-1'-phenyl]butanoxy-2,4-dimethoxy-3-methylbenzene boronic acid (major diastereomer) (147f). Yellow oil; R_f = 0.29 in 30% EtOAc/Hexanes; IR (thin film) ν 3490-3479, 2931, 1403, 1223, 1065 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.38–7.21 (m, 5H), 7.01 (s, 1H), 5.67 (s, 2H), 5.02 (d, J = 6.4 Hz, 1H), 3.94 (s, 3H), 3.68 (s, 3H), 2.19 (s, 3H), 2.04-1.96 (m, 1H), 1.76-1.68 (m, 1H), 1.34-1.21 (m, 2H), 0.94 (t, J = 7.4 Hz, 3H), 0.88 (d, J = 6.8 Hz, 3H) ppm; ^{13}C NMR ($CDCl_3$) δ 158.4, 151.4, 148.0, 140.6, 140.2, 128.1, 127.4, 127.1, 126.7, 124.5, 118.0, 84.1, 61.9, 41.4, 25.0, 15.2, 11.5, 9.5 ppm.

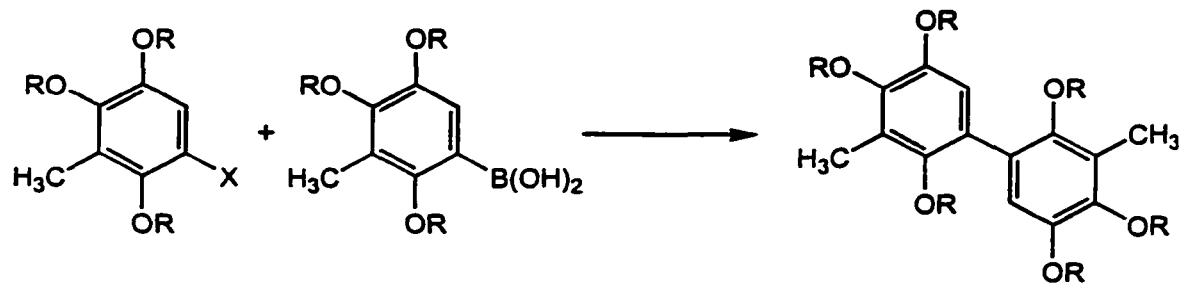


159 146g

2,5-Dibenzyloxy-4-methoxy-3-methylbenzene boronic acid (146g). Prepared using General Procedure V, white solid; mp 105-106 °C; R_f = 0.41 in 30% EtOAc/Hexanes; IR (thin film) ν 3494-3488, 3031, 2930, 1588, 1454, 1220, 1087, 1001 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.39-7.28 (m, 11H), 6.38 (s, 2H), 5.03 (s, 2H), 4.72 (s, 2H), 3.81 (s, 3H), 2.21 (s, 3H) ppm; ^{13}C NMR ($CDCl_3$) δ 157.5, 151.4, 148.6, 137.1, 136.0, 128.8, 128.6, 128.5, 128.3, 12708, 127.4, 124.9, 117.4, 77.1, 70.7, 60.3, 9.8 ppm.

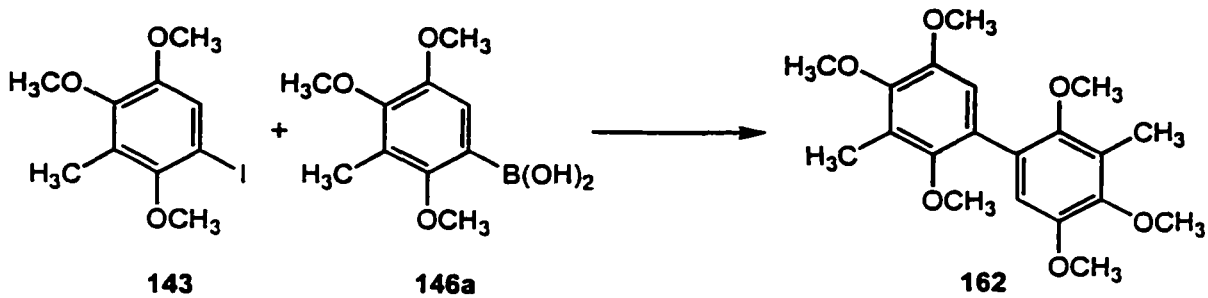


2-Benzyloxy-5-[2'-methyl-1'-phenyl]butanoxy-4-methoxy-3-methylbenzene boronic acid (major diastereomer) (**147h**). Yellow oil; R_f = 0.39 in 30% EtOAc/Hexanes; IR (thin film) ν 3522-3338, 3082, 2962, 2877, 1495, 1224, 1068, 1003 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.43–7.28 (m, 10H), 7.04 (s, 1H), 5.55 (s, 2H), 5.03 (d, J = 6.4, 1H), 4.73 (s, 2H), 3.96 (s, 3H), 2.26 (s, 3H), 2.05-1.98 (m, 1H), 1.78-1.70 (m, 1H), 1.37-1.29 (m, 1H), 0.95 (t, J = 7.5 Hz, 3H), 0.89 (d, J = 6.8 Hz, 3H) ppm.



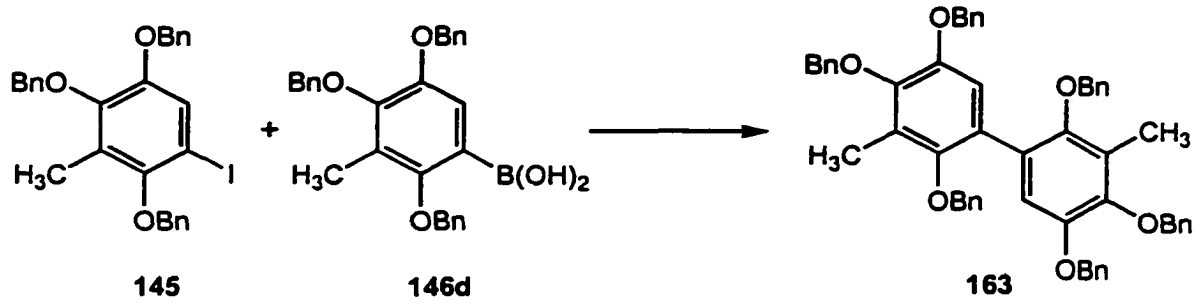
General Procedure VI (Biaryl Formation via Suzuki Coupling):

To a 0.2 M solution of boronic acid in benzene was added aryl iodide (1 eq.), tetrakis(triphenylphosphine) palladium (3%) and cesium fluoride (2.5 eq.). The mixture was refluxed for 24 h and after cooling was dissolved in EtOAc and washed with H_2O (2x) and sat. brine. The organic phase was dried over Na_2SO_4, filtered, and concentrated. Final purification by flash chromatography provided a yellow oil.

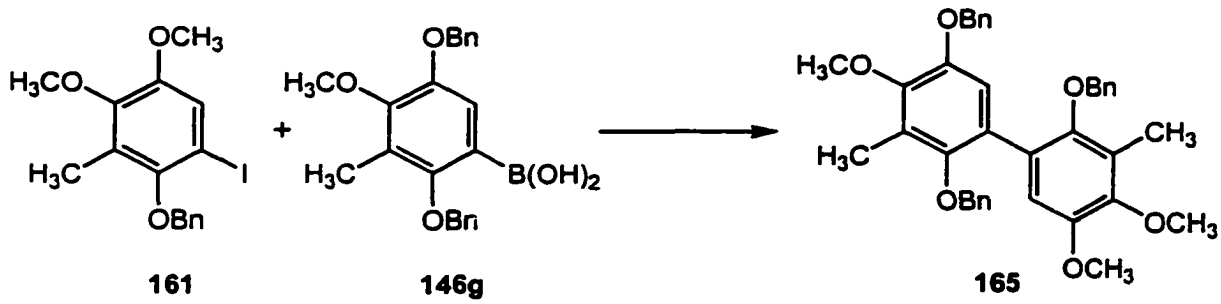


143 **146a** **162**

3,3'-Dimethyl-2,2',4,4',5,5'-hexamethoxybiphenyl (162). Yellow oil, R_f = 0.40 in 30% EtOAc/Hexanes; IR (thin film) ν 2993, 2935, 2841, 1481, 1236, 1089, 1016 cm^{-1}; ^1H NMR ($CDCl_3$) δ 6.78 (s, 2H), 3.85 (s, 6H), 3.83 (s, 6H), 3.40 (s, 6H), 2.26 (s, 6H) ppm; ^{13}C NMR ($CDCl_3$) δ 150.1, 148.6, 147.2, 126.8, 125.4, 112.3, 60.2, 60.1, 56.0, 9.6 ppm. Anal. Calcd for $C_{20}H_{26}O_6$: C, 66.91; H, 7.44. Found: C, 66.64; H, 7.24.

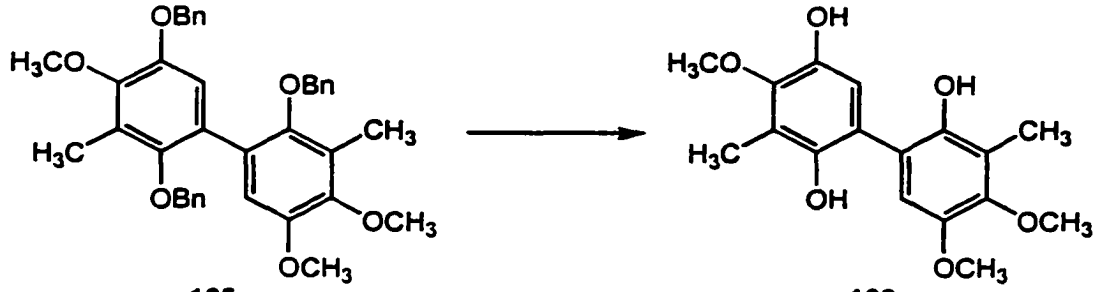


3,3'-Dimethyl-2,2',4,4',5,5'-hexabenzyloxybiphenyl (163). Yellow solid; mp 127-128 °C; R_f= 0.51 in 30% EtOAc/ Hexanes; IR (thin film) ν 3031, 2927, 1952, 1809, 1498, 1263 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.50-7.12 (m, 32H), 5.14 (s, 4H), 5.07 (s, 4H), 4.57 (s, 4H), 2.33 (s, 6H) ppm; ^{13}C NMR ($CDCl_3$) δ 149.2, 148.0, 146.7, 137.7, 137.4, 137.1, 128.4, 128.2, 128.1, 127.9, 127.8, 127.5, 126.5, 114.7, 74.9, 74.8, 71.01, 10.91 ppm. Anal. Calcd for $C_{56}H_{50}O_6$: C, 82.13; H, 6.15. Found: C, 82.17; H, 6.24.



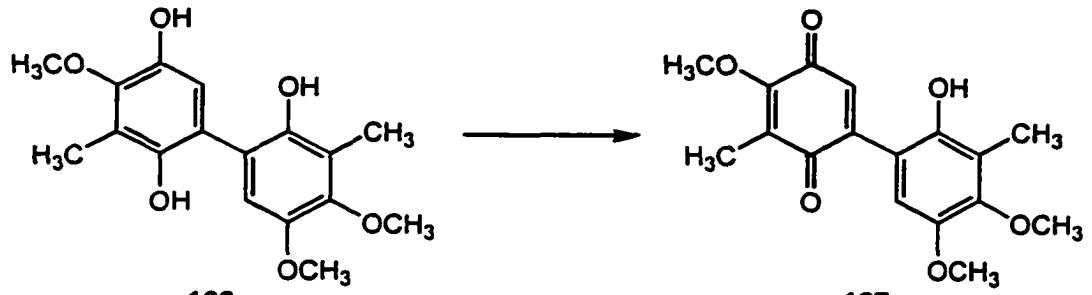
2-Methoxy-3-methyl-5-(4',5'-dimethoxy-2'-benzyloxy-3'-methylphenyl)-1,4-dihydroquinone bis(benzyl ether) (165). Yellow oil; R_f= 0.55 in 30% EtOAc/Hexanes; IR (neat) 3037, 2932, 2867, 1088, 1003 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.40-7.25 (m, 15H), 7.00 (s, 1H), 6.89 (s, 1H), 4.97 (s, 2H), 4.53 (s, 2H), 4.49 (s, 2H), 3.91 (s, 3H), 3.86 (s,

3H), 3.75 (s, 3H), 2.31 (s, 3H), 2.29 (s, 3H) ppm; ^{13}C NMR ($CDCl_3$) δ 149.1, 148.7, 148.6, 147.9, 147.7, 147.0, 137.3, 137.2, 137.1, 128.4, 128.2, 128.1, 127.8, 127.7, 127.3, 127.0, 126.9, 126.1, 126.0, 114.3, 112.2, 74.7, 74.6, 70.8, 60.4, 60.3, 55.8, 10.0, 9.9 ppm. Anal. Calcd for $C_{38}H_{38}O_6$: C, 77.27; H, 6.48. Found: C, 77.11; H, 6.71.



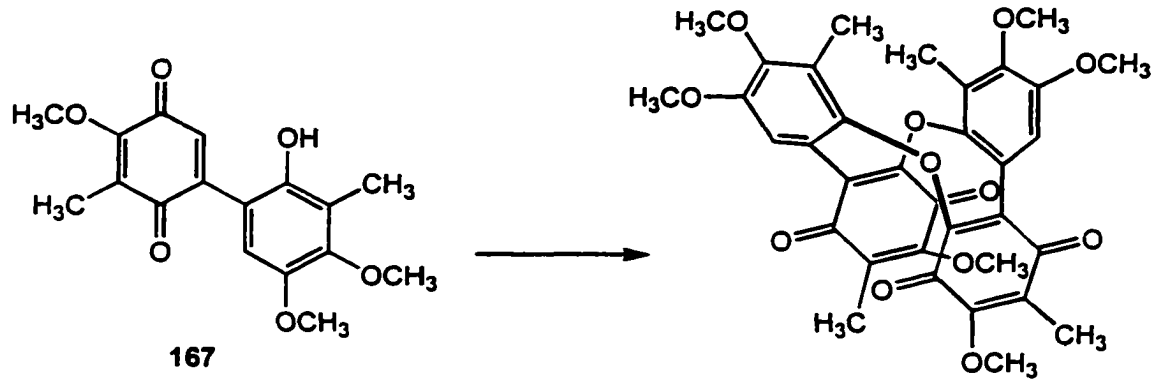
165 166

2-Methoxy-3-methyl-5-(4',5'-dimethoxy-2'-hydroxy-3'-methylphenyl)-1,4-dihydrobenzoquinone (166). To a solution of 119 mg (0.202 mmol) of biaryl **165** in EtOAc (1.0 mL) was added 12 mg of 10% Pd on activated charcoal. The contents were stirred under an atmosphere of H_2 for 12 h at which point the catalyst was removed by filtration through a Celite® pad and the solids were washed thoroughly with CH_2Cl_2. The solvent was removed *in vacuo*, and the triol was used directly without further purification. Partial characterization for the triol: colorless oil, R_f = 0.11 in 30% EtOAc/Hexanes; ^{1}H NMR ($CDCl_3$) δ 6.71 (s, 1H), 6.60 (s, 1H), 5.31 (s, 1H), 5.06 (s, 1H), 4.99 (s, 1H), 3.85 (s, 3H), 3.84 (s, 3H), 3.80 (s, 3H), 2.27 (s, 3H), 2.24 (s, 3H) ppm.

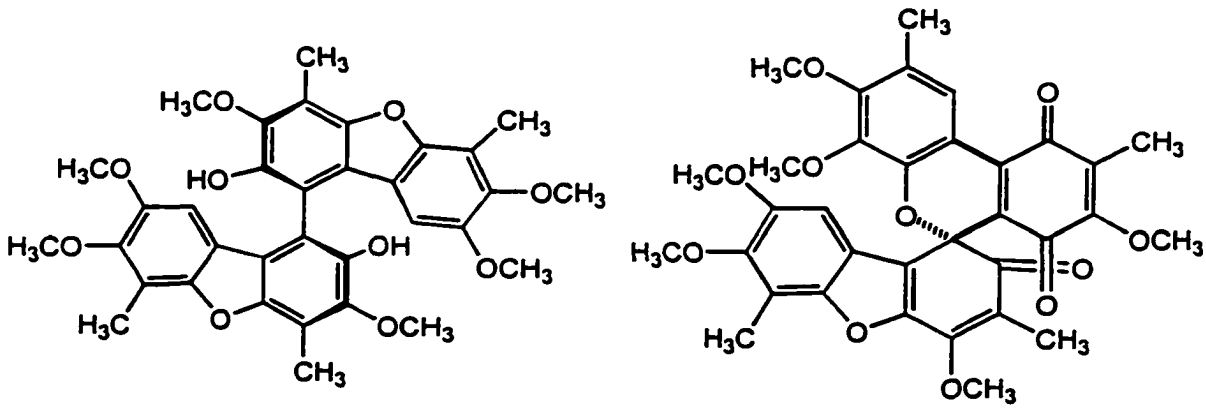


166 167

3-Methyl-2-methoxy-5-(4',5'-dimethoxy-2'-hydroxy-3'-methylphenyl)-1,4-benzoquinone (167). A solution of 0.487 g (1.52 mmol) of triol **166** in dry benzene (7.60 mL) was stirred at 0 °C while 0.346 g (1.52 mmol) of DDQ was added. After 5 min, the solvents were concentrated *in vacuo* and the remaining solid was purified by SiO_2 chromatography (10% EtOAc/Hexanes) to provide 0.388 g (80%) of **167** as a dark brown solid: mp = 57-58 °C; R_f=0.37 in 30% EtOAc/Hexanes; UV/vis (λ_{max} (ε)) 354 (3180), 280 (7730), 242 (11540); IR (thin film) 3408, 1653, 1601, 1089, 665 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.16 (s, 1H), 6.58 (s, 1H), 6.51 (s, 1H) 4.12 (s, 3H), 3.83 (s, 3H), 3.81 (s, 3H), 2.20 (s, 3H), 2.00 (s, 3H) ppm; ^{13}C NMR ($CDCl_3$) δ 190.4, 183.2, 155.7, 150.7, 147.2,147.1, 146.9, 133.0, 128.5, 122.3,116.7, 111.5, 61.1, 60.4,56.3, 9.54, 9.11 ppm. Anal. Calcd for $C_{17}H_{18}O_6$: C, 64.14; H, 5.70. Found: C, 64.05; H, 5.75.



167 173



174 175

Acid-Catalyzed Cyclization of Hydroxyquinone: A solution of 100 mg (0.314 mmol) of **167** and 3.0 mg (0.012 mmol) of PPTS in benzene (2.0 mL) was heated and maintained at a gentle reflux in air for 36 h. The solvent was removed in vacuo, and the residue was purified by SiO_2 chromatography (10% EtOAc/Hexanes) to provide dimers **173** (10.1 mg, 10%), **174** (29.6 mg, 30%), **175** (17.7 mg, 18%).

3,7,8,12,16,17-Hexamethoxy-2,6,11,15-tetramethyl-1,4,10,13-tetraoxotetrabenzo-[*b,d,g,i*][5,14]dioxacyclodecene (173). Orange solid, mp 104-105 °C; R_f = 0.51 in 30% EtOAc/Hexanes; UV/vis (λ_{max} (ε)) 462 (4800), 326 (7780), 252 (34300); IR (thin film) ν 1667, 1656, 1115, 1088, 671 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.36 (s, 2H), 4.06 (s, 6H), 3.93 (s, 6H), 3.85 (s, 6H), 2.45 (s, 6H), 2.03 (s, 6H) ppm; ^{13}C NMR ($CDCl_3$) δ 184.2, 172.6, 155.8, 152.9, 151.5, 150.5, 149.6, 129.5, 122.6, 117.4, 117.2, 100.6, 61.3, 60.9, 56.1, 9.04, 8.84 ppm; HRMS *m/e* calcd for $C_{34}H_{33}O_{12}$ (MH^+) 633.1973, found 633.1972.

2,2'-Dihydroxy-3,3',7,7',8,8'-hexamethoxy-4,4',6,6'-tetramethyl-1,1'-bidibenzofuran (174). Colorless oil; R_f = 0.13 in 30% EtOAc/Hexanes; UV/vis (λ_{max} (ε)) 312 (38300), 242 (36400); IR (neat) ν 3434, 3005, 1099, 1001, 757 cm^{-1}; ^1H NMR ($CDCl_3$) δ 6.14 (s, 2H), 5.58 (s, 2H, exchanges with D_2O), 3.96 (s, 6H), 3.73 (s, 6H), 3.40 (s, 6H), 2.64 (s, 6H), 2.45 (s, 6H) ppm; ^{13}C NMR ($CDCl_3$) δ 150.7, 149.8, 149.2, 146.9, 144.7, 143.0, 119.1, 118.7, 115.7, 115.2, 110.4, 101.0, 61.5, 60.7, 55.7, 9.70, 9.13 ppm; HRMS *m/e* calcd for $C_{34}H_{33}O_{12}$ (M^+) 602.2181, found 602.2133.

2,7-Dimethyl-3,8,9-trimethoxy-6-oxa-1,4-phenanthraquinone-5-spiro-1'-(4',6'-dimethyl-3',7',8'-trimethoxy)dibenzofuran-2'(1'*H*)-one (175). Brown oil; R_f = 0.45 in 30% EtOAc/Hexanes; UV/vis (λ_{max} (ε)) 552 (1540), 410 (6080), 356 (6110), 282 (9560), 242 (17300); IR (neat) ν 3001, 1681, 1649, 1115, 1091, 754 cm^{-1}; ^1H NMR ($CDCl_3$) δ 8.05 (s, 1H), 5.74 (s, 1H), 3.91 (s, 3H), 3.88 (s, 3H), 3.87 (s, 3H), 3.77 (s, 3H), 3.71 (s, 3H), 3.41 (s, 3H), 2.38 (s, 3H), 2.36 (s, 3H), 1.95 (s, 3H), 1.88 (s, 3H) ppm; ^{13}C NMR ($CDCl_3$)

δ 192.4, 187.5, 180.3, 154.8, 151.9, 150.5, 149.7, 149.6, 148.3, 147.4, 146.7, 145.6, 132.8, 132.7, 130.4, 128.6, 121.8, 120.4, 116.2, 116.0, 111.9, 109.0, 98.9, 76.3, 61.0, 60.8, 60.6, 60.2, 56.0, 55.6, 10.3, 9.00 ppm; HRMS *m/e* calcd for $C_{34}H_{33}O_{11}$ (MH^+) 617.2023, found 617.2029.

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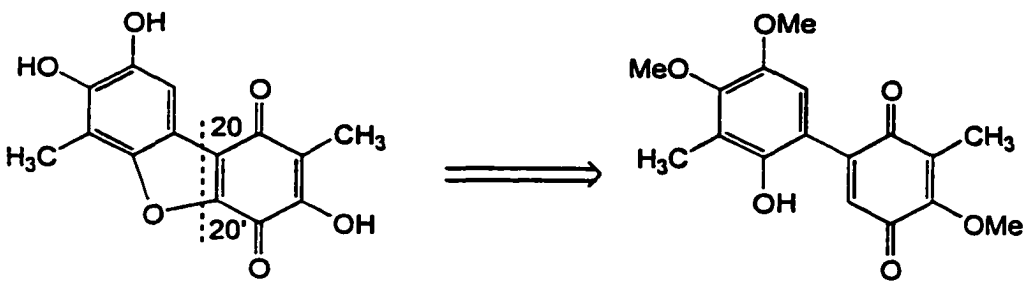
Chapter 2

Mechanistic Considerations and Application of Reductive Cyclizations to Simple Systems

Introduction

Our approach to the central aromatic core of popolohuanone E entailed the formation of the central furan ring via the conjugate addition of the phenolic hydroxy of **167** to the quinone followed by an oxidation of the intermediate dihydroquinone (Scheme XXXIII). However, when **167** was subjected to mildly acidic conditions, several compounds were obtained, all of which were dimeric and were believed to have come from a series of electron transfer reactions,[82] common processes in quinone cyclization reactions.[83] The utility of this cyclization could be better determined once the mechanistic processes leading to the products were understood.

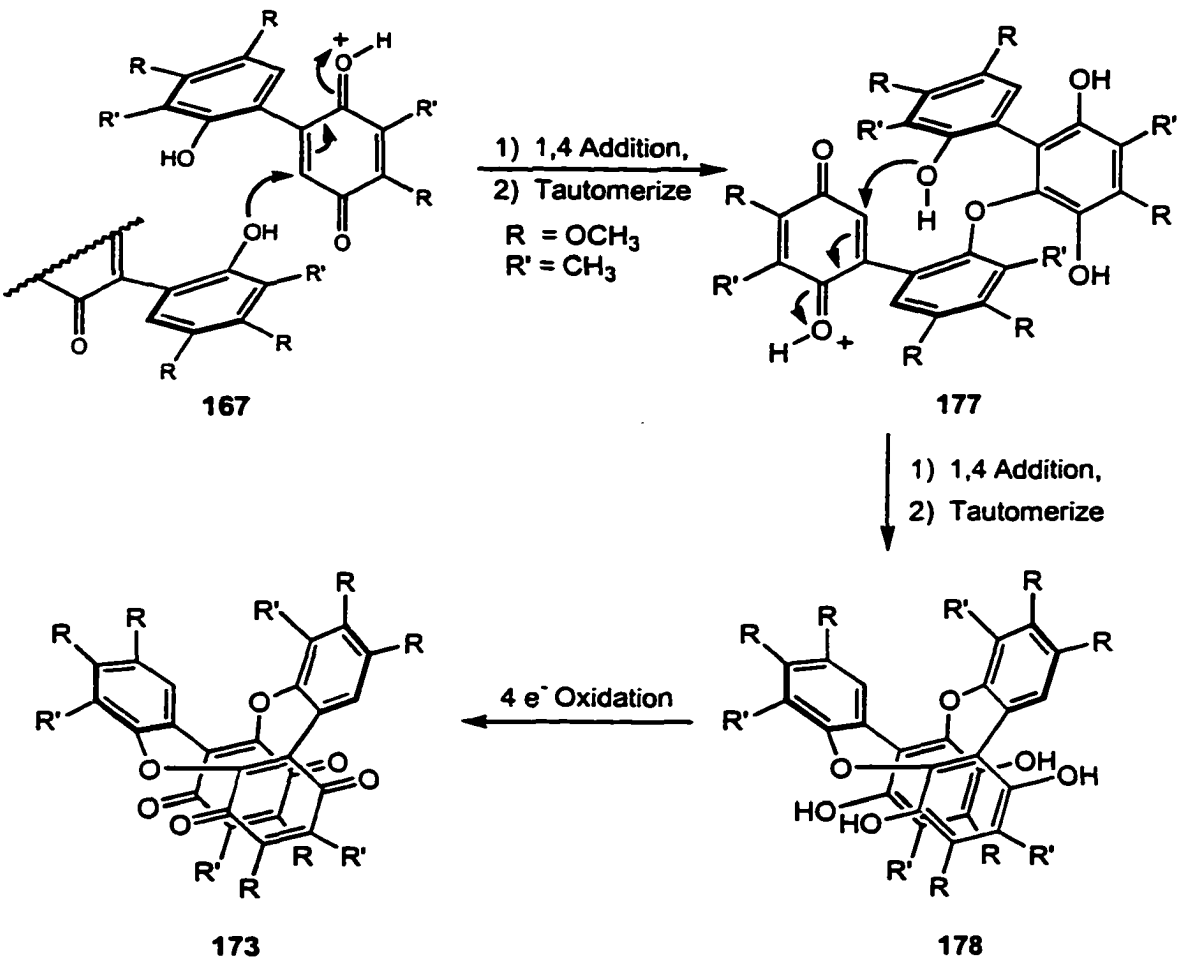


Scheme XXXIII

Mechanistic Considerations

From a structural analysis of the dimers, it was evident that both intra- and intermolecular processes were occurring. Since two of the structures had retained their quinone functionalities (**173**, **175**) and one had not (**174**), the proposed mechanisms would involve internal redox chemistry or the reaction of adventitious O_2.

The formation of dimer **173** was believed to have originated from sequential 1,4-addition steps. The intermolecular 1,4-addition of the hydroxyl functionality to the quinone portion would form an ether linkage that after tautomerization would provide **177** (Scheme XXXIV). This system could easily undergo an intramolecular 1,4-addition that after tautomerization would provide the bis-dihydroquinone dimer **178**. A subsequent four-electron oxidation would provide the bis-quinone product **173**. The saddle conformation was determined to be the lowest energy conformer for this dimer using Spartan.[84]



Scheme XXXIV

The mechanistic determination for dimers **174** and **175** required an examination of the options available to the starting material. The intramolecular addition of the hydroxyl group of **167** to the quinone could occur by two routes, the desired 1,4-conjugate addition and a 1,2-addition to the activated carbonyl (Figure 31). According to Baldwin's rules of ring closure,[78] the 1,4-intramolecular addition is a kinetically disfavored 5-*endo*-trig cyclization whereas the 1,2-addition of the hydroxyl to the activated carbonyl would produce hemiketal **180** through a favorable 5-*exo*-trig process.

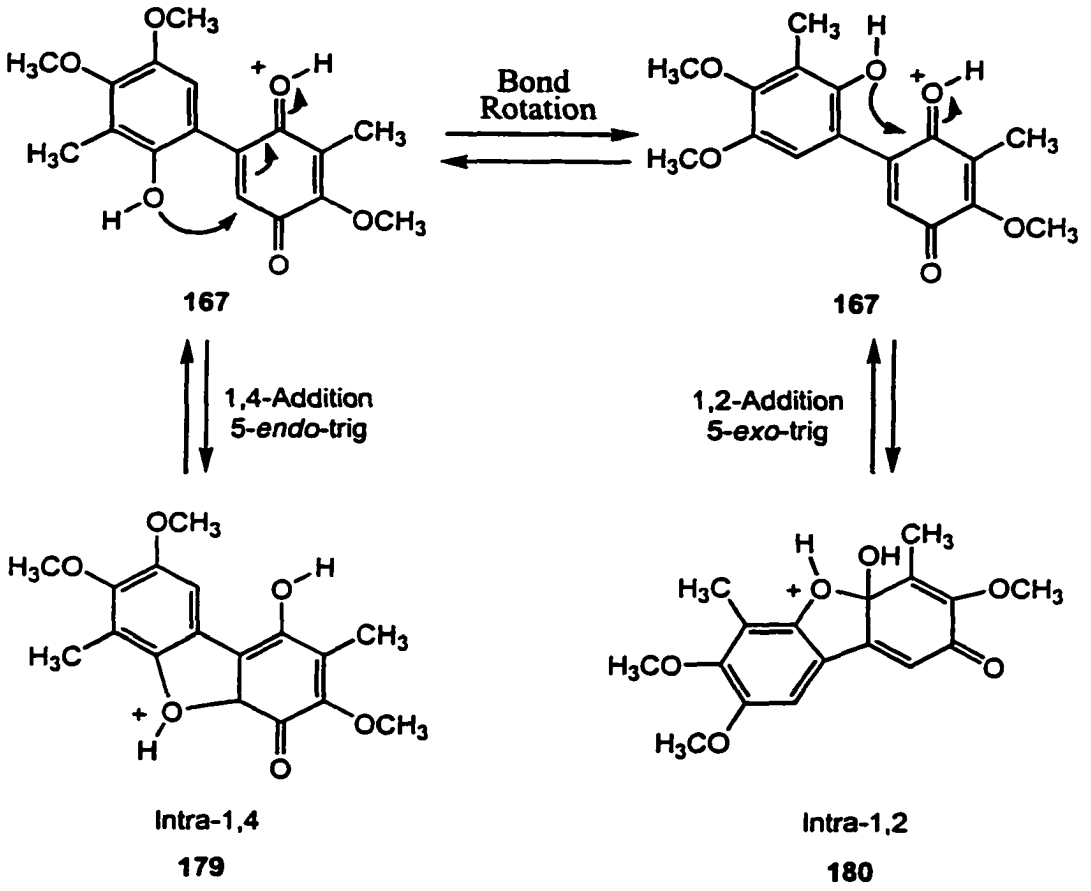
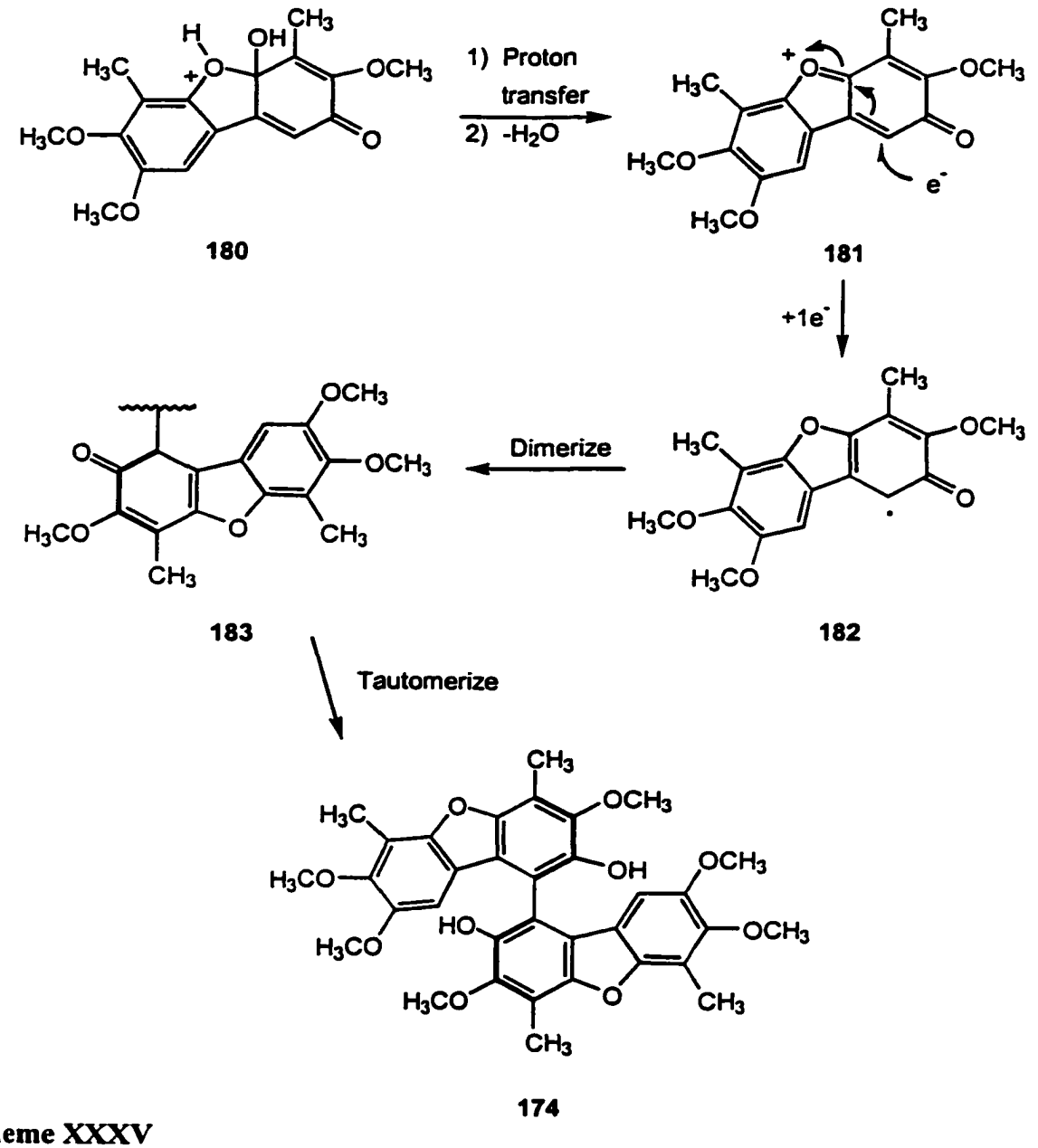


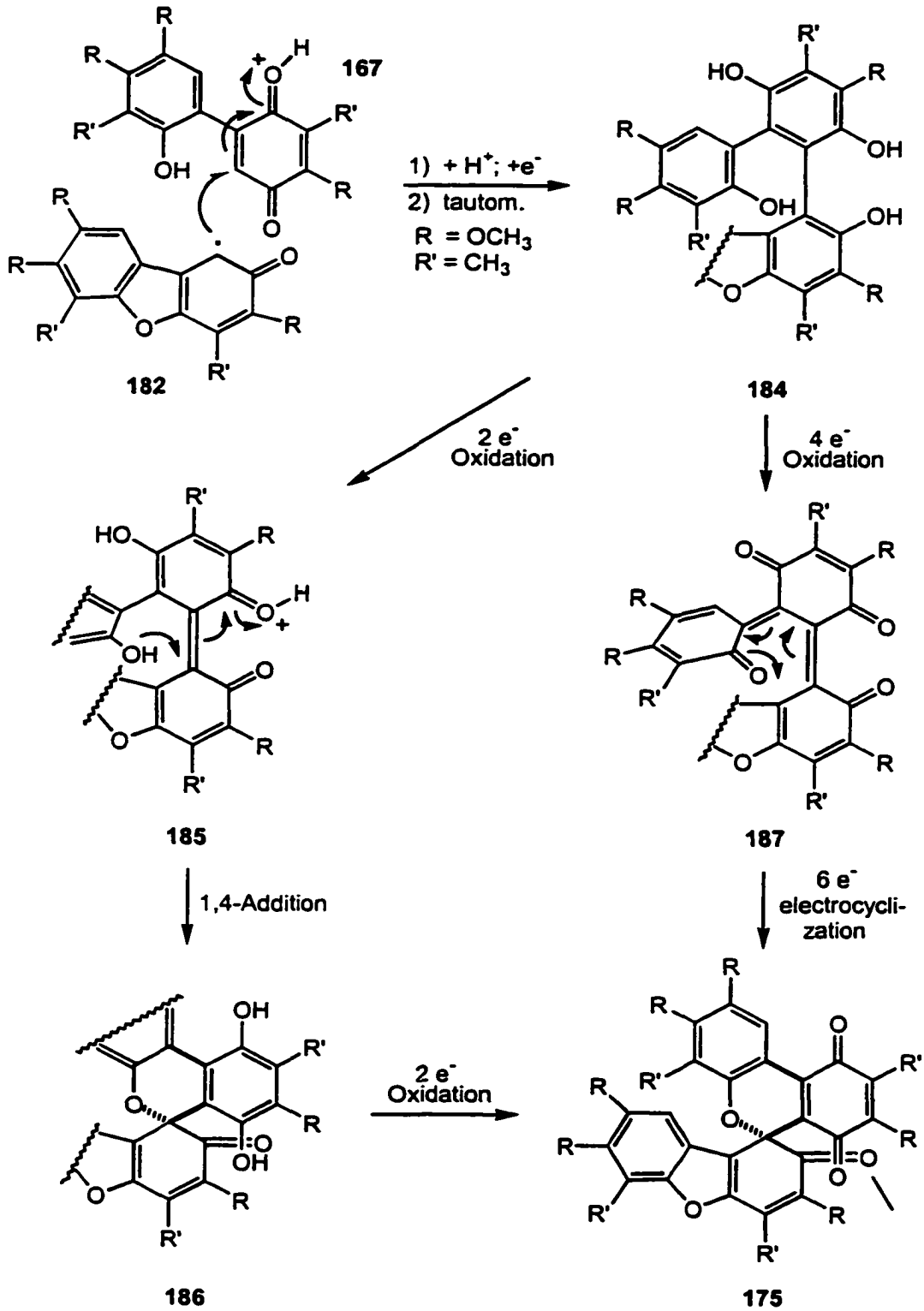
Figure 31

Based on this evaluation, dimers **174** and **175** could have been formed via a 1,2-intramolecular process that involved the intermediate hemiketal **180**. Since the reaction is performed using a catalytic amount of PPTS, only a small amount of the hemiketal exists in equilibrium with the starting material at any one time. After transferring a proton to **180** and the subsequent loss of H_2O, the oxonium intermediate **181** could have formed (Scheme XXXV). A single electron transfer to this quinone-like molecule would reduce it to form the ketone-stabilized radical **182**. A subsequent dimerization/ tautomerization process would furnish the symmetrical dimer **174**.



Scheme XXXV

The structure of spiro-dimer **175** appears to be a hybrid of both **173** and **174**. The addition of the ketone-stabilized radical intermediate **182** to the starting material **167** (Scheme XXXVI) followed by tautomerization would provide dihydrodimer **184**.



Scheme XXXVI

The subsequent oxidation could proceed by two routes: a two-electron oxidation to give the semiquinone intermediate **185** or a four-electron oxidation to provide the oxaquinodimethane **187**. From **185**, a 1,4-intramolecular addition would give dihydroquinone **186** that would provide **175** after a two-electron oxidation. Alternatively, the intermediate **187** could suffer an electrocyclic ring closure that would generate the spiro-dimer **175** directly.

The PPTS induced cyclization of hydroxyquinone **167** uncovered a complex redox process from which several interrelated products were formed (Figure 32). In the presence of a proton source, the starting material **167** exists in equilibrium with the intramolecular-1,2-oxonium intermediate **180**, a material that cannot react further without an electron source. The intermolecular 1,4-bisdihydroquinone dimer **178** formed slowly (as observed by TLC analysis), but once formed, it could act as a possible internal reducing agent for the oxonium to produce the intramolecular 1,2-addition-derived radical intermediate **182**. As a consequence of it being a reducing agent, dihydrodimer **178** is oxidized to the bis-quinone **173**.

The radical intermediate **182** has several pathways to follow. By reacting with itself, it forms the dimer **174**. By adding to the starting material, the spiro-dimer **175** is formed. This intermediate likely plays an important role in the formation of the as-of-yet undetermined product mixture **176.**

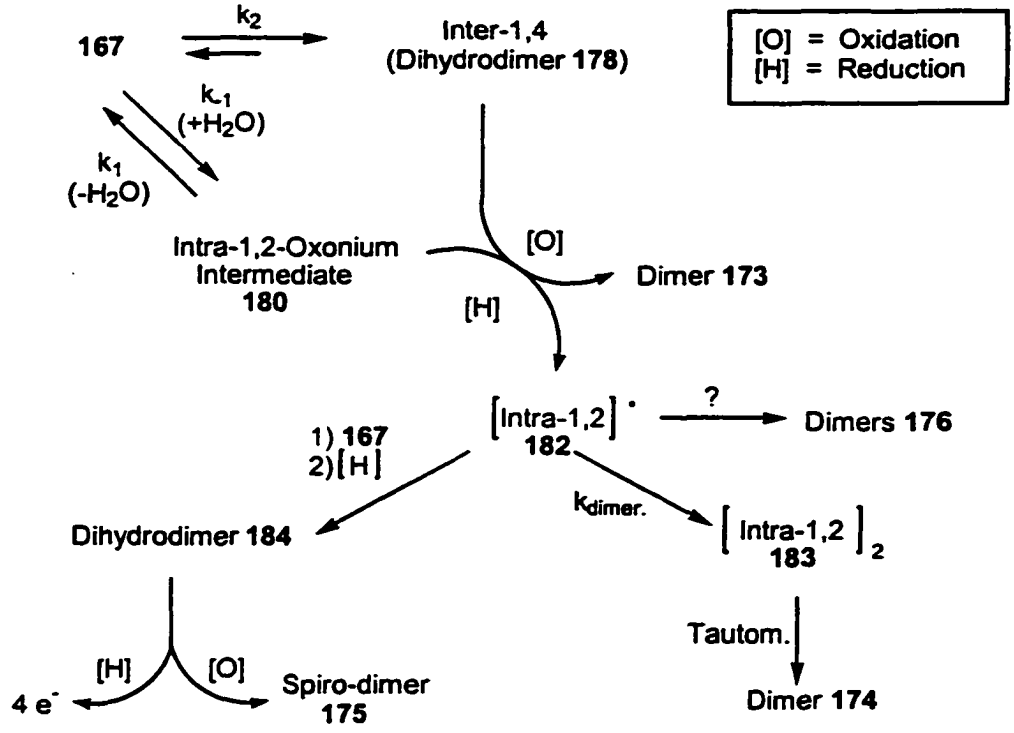
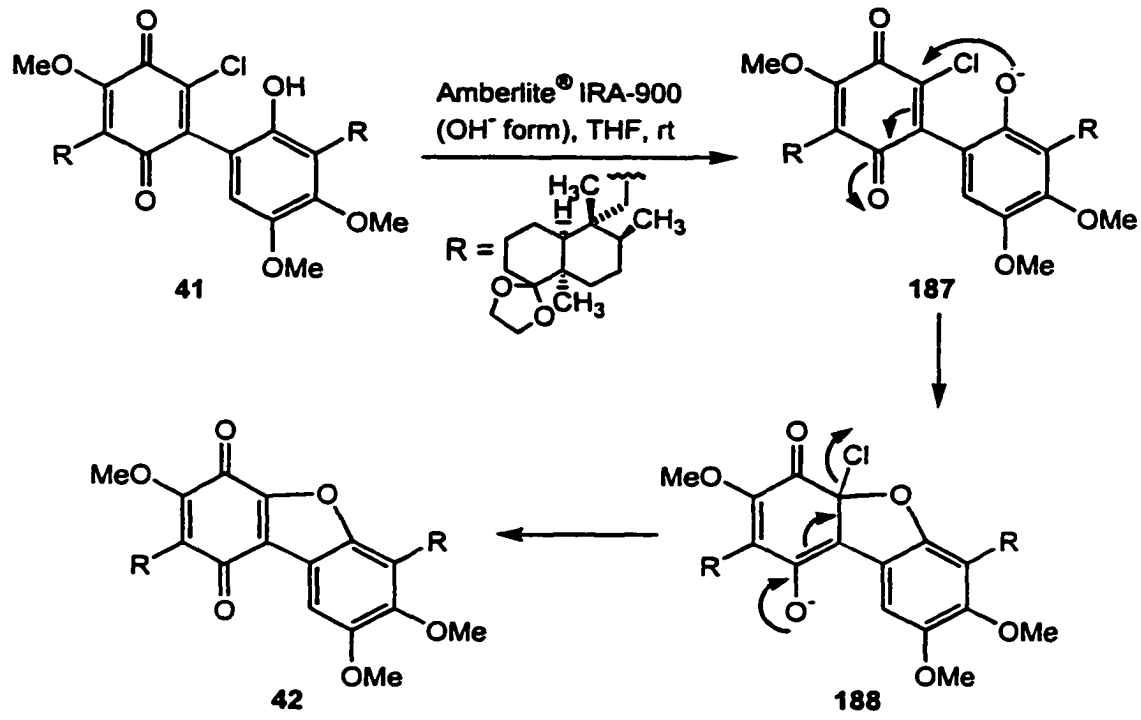


Figure 32

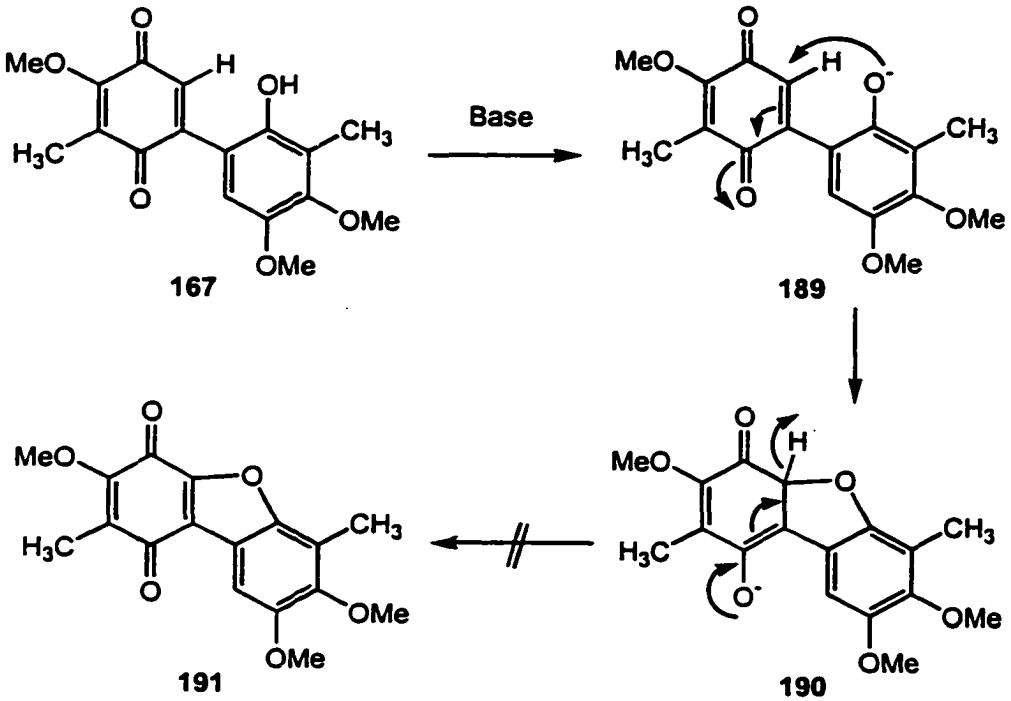
With a better understanding of how the dimeric products from the acid catalyzed cyclization of **167** may have formed, one major question remained. Why was Terashima's dibenzofuran formation successful for substrate **41** and unsuccessful for our compound **167**? A mechanistic study of these transformations allows for their differentiation.

For Terashima's cyclization (Scheme XXXVII), the 1,4-intramolecular addition of the phenoxide anion **187** to the chloroquinone portion gives intermediate **188**. This intermediate can either revert to starting material or displace a chloride anion, a relatively good leaving group, to regenerate the quinone portion and provide the dibenzofuran **42**.



Scheme XXXVII

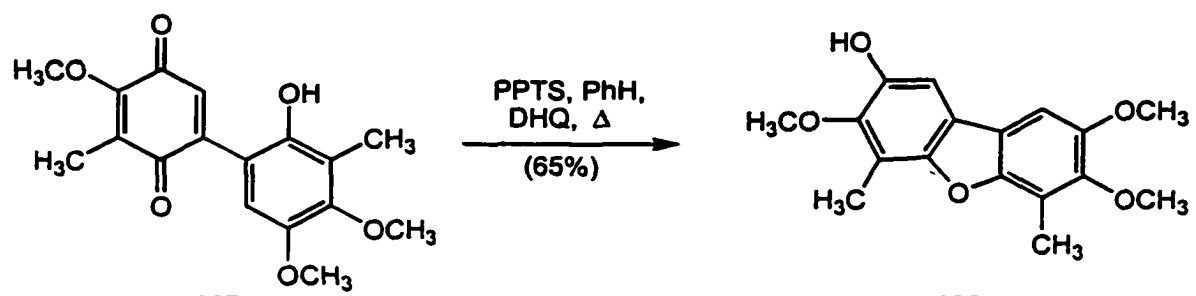
However, for our substrate, **167**, the 1,4-intramolecular addition of the phenoxide anion **189** would provide an intermediate **190** (Scheme XXXVIII). This intermediate can only revert to starting material without a leaving group present. Based on this analysis, the 1,4-intramolecular addition is not a viable process.



Scheme XXXVIII

Results and Discussion

The formation of the cyclized products was dependent upon the presence of bisdihydroquinone **178** as an internal reducing agent. The ability to direct the reaction towards the 1,2-addition pathway was analyzed by incorporating an external reducing agent. The introduction of 1,4-dihydroquinone (DHQ) to the reaction led to the formation of a single new product within one hour. This product was identified as dibenzofuran **192**, the monomeric form of **174** derived from the intramolecular 1,2-addition pathway (Scheme XXXIX). That a monomeric product was isolated suggests that the lifetime of the semiquinone radical **182** in the presence of a small reducing agent (DHQ) is short relative to when a sterically hindered dihydroquinone **178** acts as the reducing agent.



167 **192**

Scheme XXXIX

Since the addition of a reducing agent directed the reaction towards the 1,2-addition pathway, it was anticipated that the addition of an oxidizing agent might lead to products derived from the 1,4-addition pathway. However, the addition of 1,4-benzoquinone provided all of the dimeric products previously observed. This might have

been a function of the oxidizing power of 1,4-benzoquinone.[85]

Silver oxide is known to perform oxidations through a radical mechanism[86] and could form an alkoxyl radical initially that could undergo either a 1,4-intra- or a intermolecular addition reaction. However, the formation of the 5-membered furan ring should be a more favorable process under the conditions of this reaction.[87] Interestingly, the addition of silver oxide[88] (Ag_2O) afforded a new product **193** (66%) in addition to the 1,4-intramolecular dimer **173** (10%). Since dimer **173** was one of the products from both the silver oxide (minor product) reaction and the acid catalyzed reaction, it might have been possible that the major product also may have come from this 1,4-intramolecular addition.

The determination of the structure for the product **193** required the 2D NMR techniques previously outlined. Compound **193** was dimeric (*m/e* = 632) based upon the high-resolution mass spectrum, and the IR spectrum showed stretches indicative of a quinone at 1675 cm^{-1} but with no hydroxyl stretches (3550-3200 cm^{-1}). Because only 17 carbons were present in the ^{13}C NMR spectrum, the product was assumed to be symmetrical.

The HMQC data was used to determine the specific carbon-proton attachments (Table 9). The C-1 carbon (δ 111.2) corresponded to the aromatic proton that resonated at δ 6.26, but unlike the previous analyses, the NOESY displayed no proximal methoxy protons nor did the COSY give any long-range couplings. Fortunately, the HMBC study provided some information, including couplings between the C-1 carbon and the C-8, C-11, C-12, and C-13 carbons (δ 143.9, 148.6, 119.2, 148.9, respectively).

Table 9

Spectral Data for Compound **193**

C #	HMQC ^{1}H	HMQC ^{13}C	COSY (H/H)	NOESY (H/H)	HMBC (50 ms)	HMBC (100 ms)
1	6.26	111.2	-	-	12; 11	8; 13
2	3.99	60.9	-	-	-	15
3	3.66	56.0	-	-	7; 13	13
4	3.64	60.1	-	-	12	12
5	1.96	9.31	5/2	5/2	10; 15; 17	10; 15; 17; 16
6	1.86	9.86	6/1	6/4; 6/1	9; 11; 12	9; 11; 12
7	-	116.2	-	-	-	-
8	-	119.2	-	-	-	-
9	-	122.7	-	-	-	-
10	-	129.5	-	-	-	-
11	-	143.9	-	-	-	-
12	-	148.6	-	-	-	-
13	-	148.9	-	-	-	-
14	-	150.0	-	-	-	-
15	-	154.4	-	-	-	-
16	-	177.6	-	-	-	-
17	-	186.5	-	-	-	-

An HMQC analysis of the C-6 methyl (δ 9.86) showed that it correlated with the methyl signal that resonated at δ 1.86 and displayed long-range coupling to the aromatic proton resonating at δ 6.26 (C-1) in the H/H COSY. However, the NOESY analysis indicated proximity to this same aromatic proton and this complicated the analysis. Ultimately it was assumed to have been a coupling constant that "bled through" the spectrum.[89] The NOSEY spectrum did indicate that the C-6 methyl group was proximal to the methoxy group resonating at δ 3.64 (C-4) and the HMBC analysis established couplings to the

carbons resonating at δ 122.7 (C-9), δ 143.9 (C-11), and δ 148.6 (C-12). By HMQC, it was established that the methoxy carbon resonating at δ 60.1 (C-4) corresponded with the protons at δ 3.64 and an HMBC analysis determined that it was attached to the aromatic ring at the carbon resonating at δ 148.6 (C-12). The C-3 methoxyl group displayed couplings in the HMBC analysis that established an attachment to the aromatic ring by the carbon resonating at δ 148.9 (C-13). This combined information allowed for the partial assignment of the aromatic ring **A** shown in Figure 33.

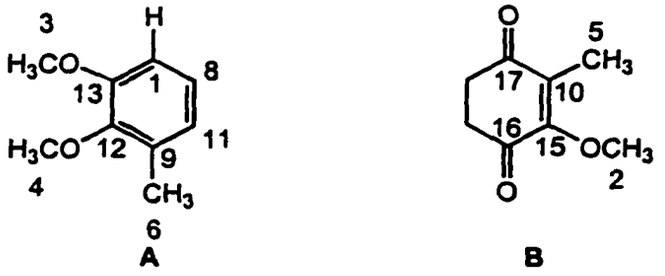
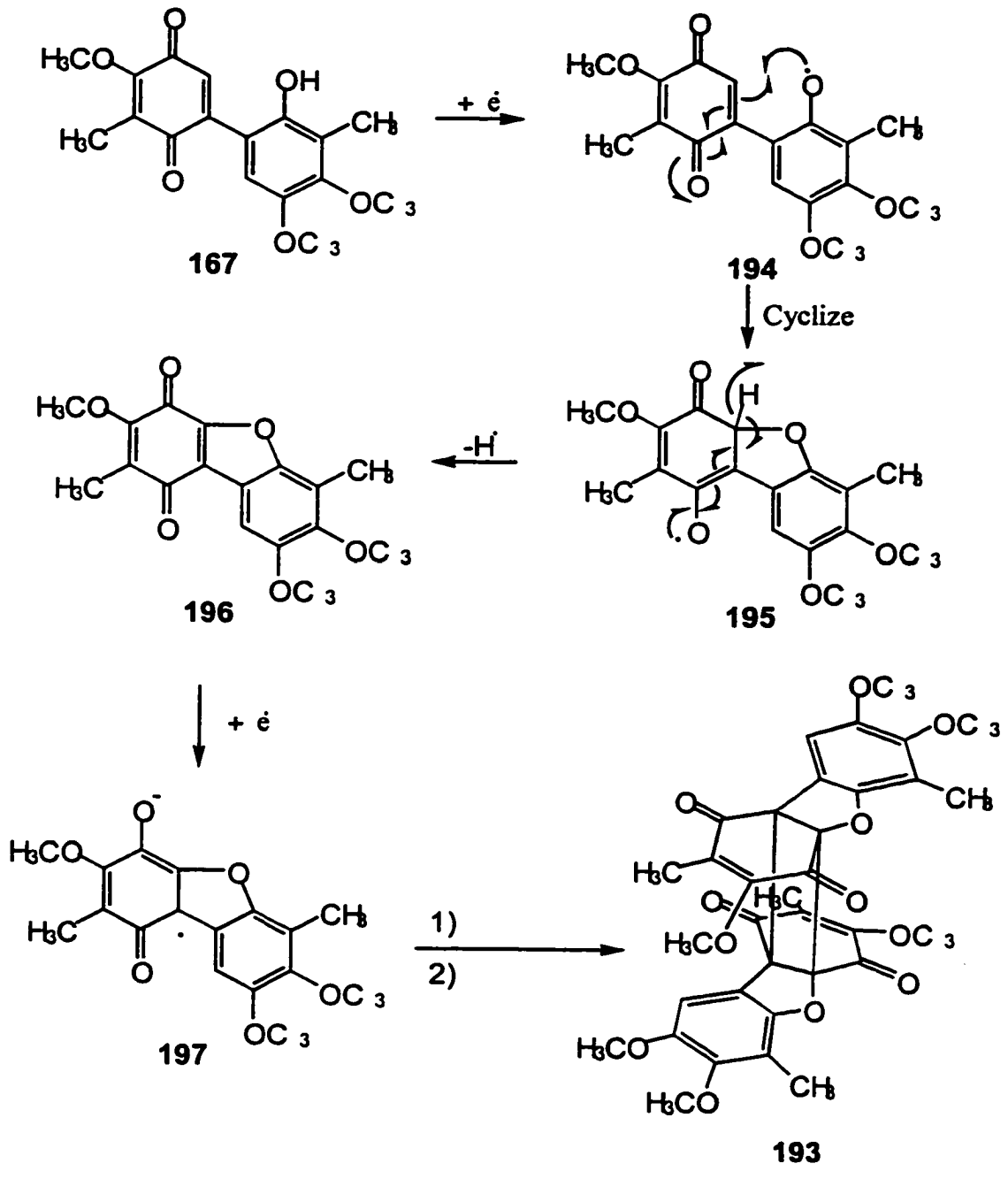


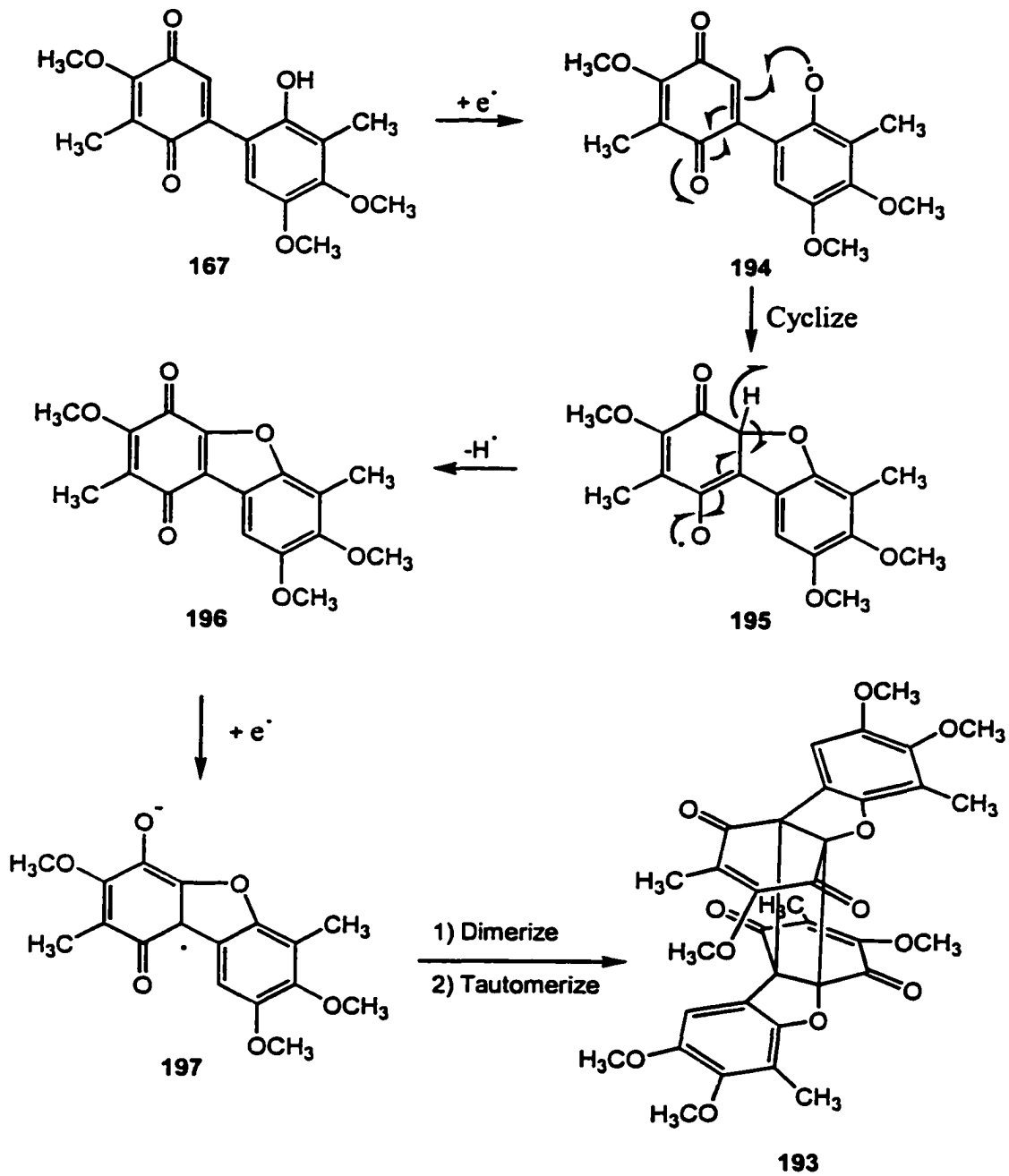
Figure 33

The methyl carbon resonating at δ 9.31 (C-5) was linked to the protons at δ 1.96 by HMQC analysis, and the COSY and NOESY analyses displayed weak couplings between the C-5 methyl and the methoxyl group resonating at δ 3.99 (C-2). The HMBC data for the C-5 methyl group allowed for the assignation of the aromatic carbons resonating at δ 129.5 (C-10), δ 154.4 (C-15) and the carbonyl carbons resonating at δ 177.6 (C-16) and δ 186.5 (C-17) to this ring system. The C-2 methoxyl group also displayed coupling to the carbon resonating at δ 154.4 (C-15) that, in combination with the other data, allowed for a partial assignment of the aromatic ring **B** in Figure 33.

While the information from the 2-D analyses was valuable for the determination of the structure of **193**, it did not allow for an overall assignment. However, by combining the spectral data with the known reactivity of phenols to silver oxide, a plausible structure could be proposed.

The addition of the alkoxyl radical **194** to the quinone (Scheme XL) would form intermediate **195**. After proton abstraction, the dibenzofuranoquinone **196** would form the trimethyl ether of the aromatic core of popolohuanone E. However, the excess silver oxide allowed for an environment rich with radicals that would be trapped by the dibenzofuranoquinone **196** and subsequent dimerization would produce **193**. Since light was never excluded from the reaction set-up, it is possible that these types of compounds might have also undergone 2+2 chemistry.

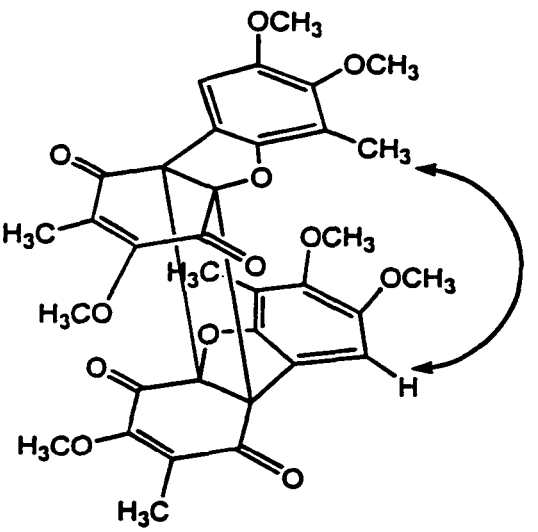




Scheme XL

The radical anion **197** has several dimerization pathways available to it and only one is illustrated in Scheme XL. If the NOESY couplings between the aryl proton and the aryl methyl were genuine and not an artifact, product **198** would be another possible

product from the dimerization of **196** (Figure 34). Lacking 2-D ^{13}C NMR data that would indicate the connectivity between ring systems, an exact structure for this product could not be determined. Attempts to obtain an X-ray crystal structure failed due to insufficient crystal quality.



198

Figure 34

The implications of alkoxyl radical intermediates in the Ag_2O reaction were not previously considered when determining the structures for the mixture of dimers **176**. The alkoxyl radical **194** could also have been an intermediate generated from the electrons liberated from the oxidation of bis-dihydroquinone dimer **178**. This would have led to intermediate **197** that could have combined with the ketone stabilized radical intermediate **186** giving the dimers **176**, all of which would be unsymmetrical (Figure 35).

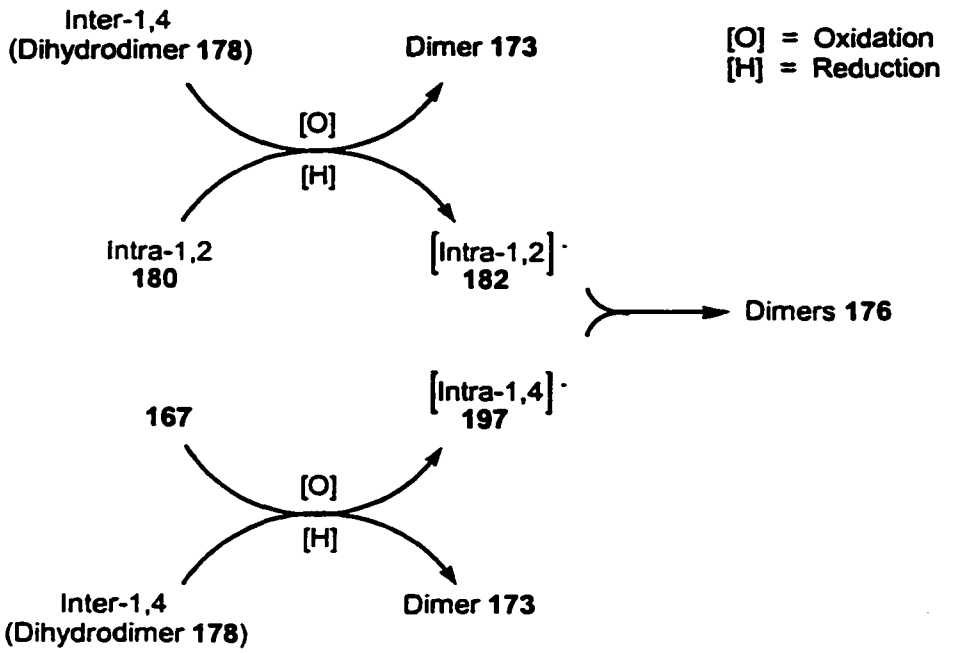
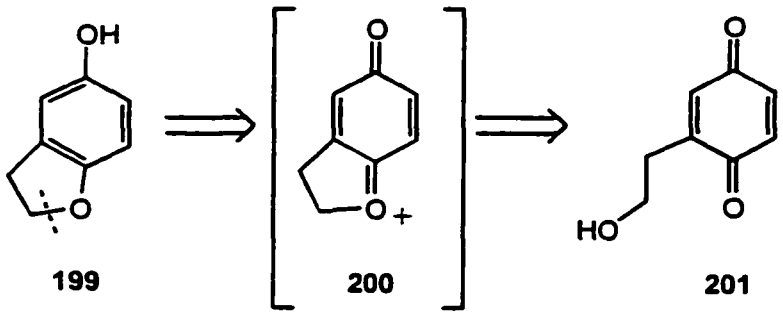


Figure 35

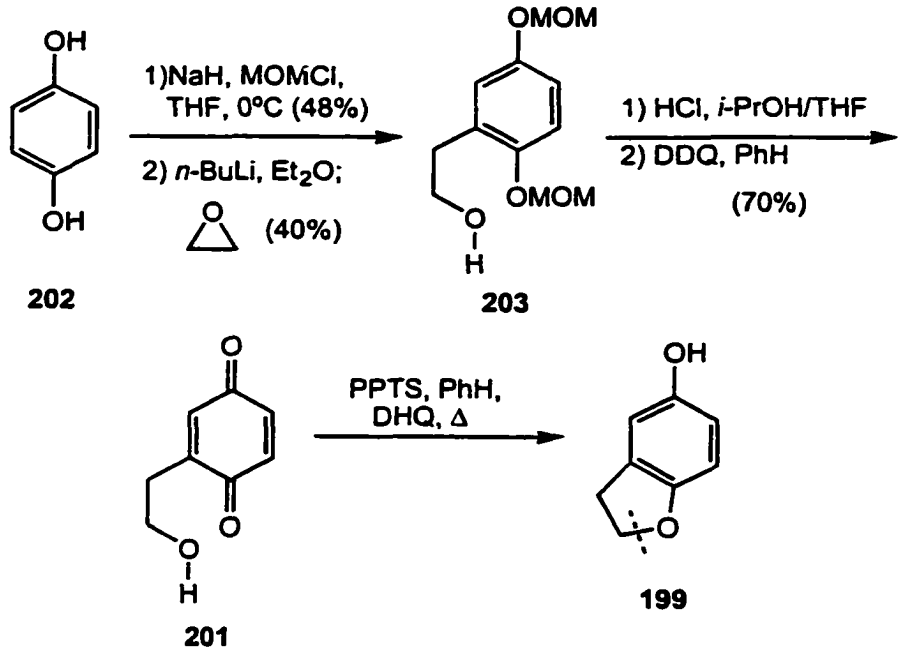
Because of the success of the 1,2-intramolecular process under reducing conditions, the addition of DHQ was investigated with other model systems to determine the general utility for generating dihydrobenzo-furan systems. From a retrosynthetic standpoint, the benzofuran **199** could be formed via the oxonium intermediate **200** which itself would be generated from an acid catalyzed cyclization of a β-hydroxyethyl quinone **201** (Scheme XLI).



199 200 201

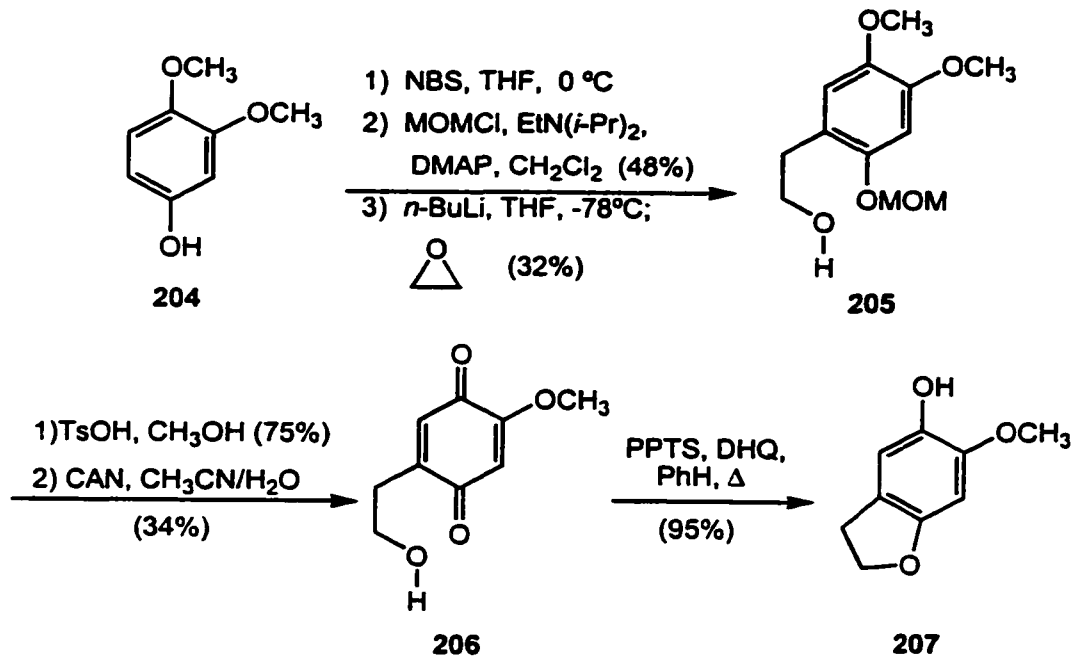
Scheme XLI

Procurement of the 2-(2'-hydroxyethyl) quinone substrate **201** was straight forward. Bis-protection of 1,4-dihydroquinone was achieved with chloromethyl methyl ether (MOMCl) and the hydroxyethyl group was introduced by lithiation and alkylation with ethylene oxide to provide **203** (Scheme XLII). Subsequent deprotection under acidic conditions (PPTS, CH_3OH) and oxidation with 2,3-dichloro-5,6-dicyano-1,4-benzoquinone[90] (DDQ) provided **201**. Exposure to the cyclization conditions provided only the desired dihydrobenzofuran **199**.[91]

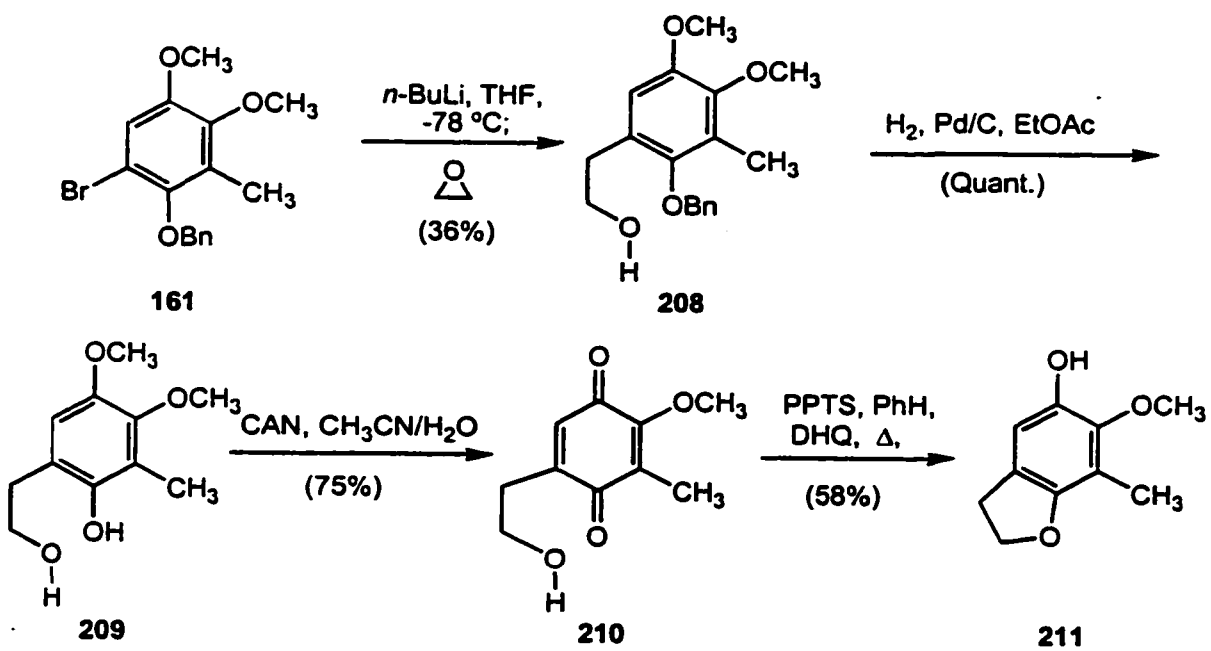


Scheme XLII

More substituted examples included 2-(2'-hydroxyethyl)-5-methoxy-1,4-benzoquinone **206** (Scheme XLIII) and 2-(2'-hydroxyethyl)-5-methoxy-6-methyl-1,4-benzoquinone **210** (Scheme XLIV) were generated in a similar fashion to **201** and the cyclizations to form the simpler benzofurans worked well (58-95%).

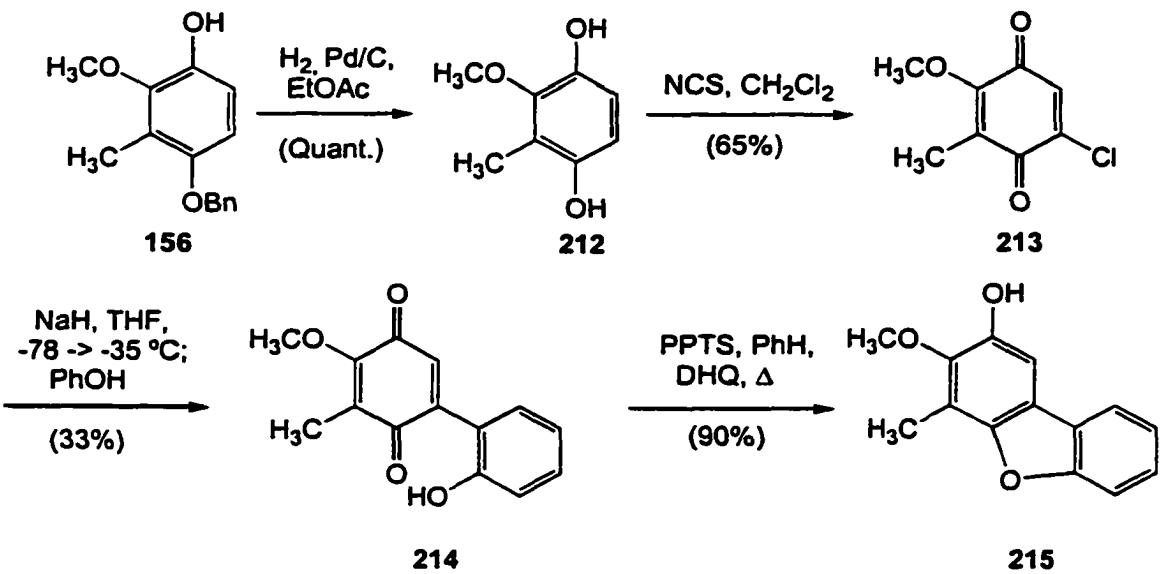


Scheme XLIII



Scheme XLIV

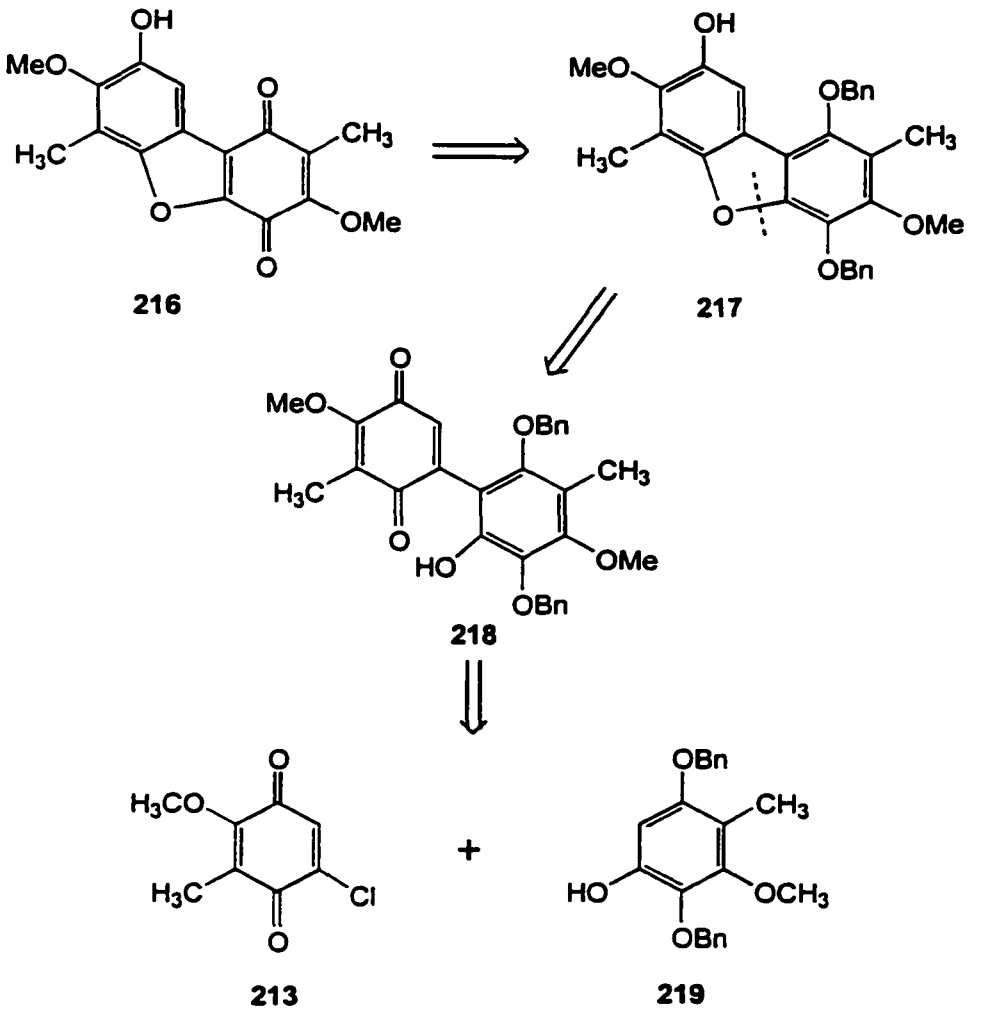
A more relevant application of this method to the current problem would be with 2-(2'-hydroxyphenyl)-5-methoxy-6-methyl-1,4-benzoquinone **215** for the generation of dibenzofurans. The synthesis of dibenzoquinone **215** (Scheme XLV) required that phenol **156** be debenzylated to provide dihydrobenzoquinone **212** which was then subjected to NCS to provide chloroquinone **213**. The quinone was added to preformed sodium phenoxide to generate adduct **214** as a single product from C-alkylation. Subjection of **214** to the standard cyclization conditions afforded **215** in high yield (90%).



Scheme XLV

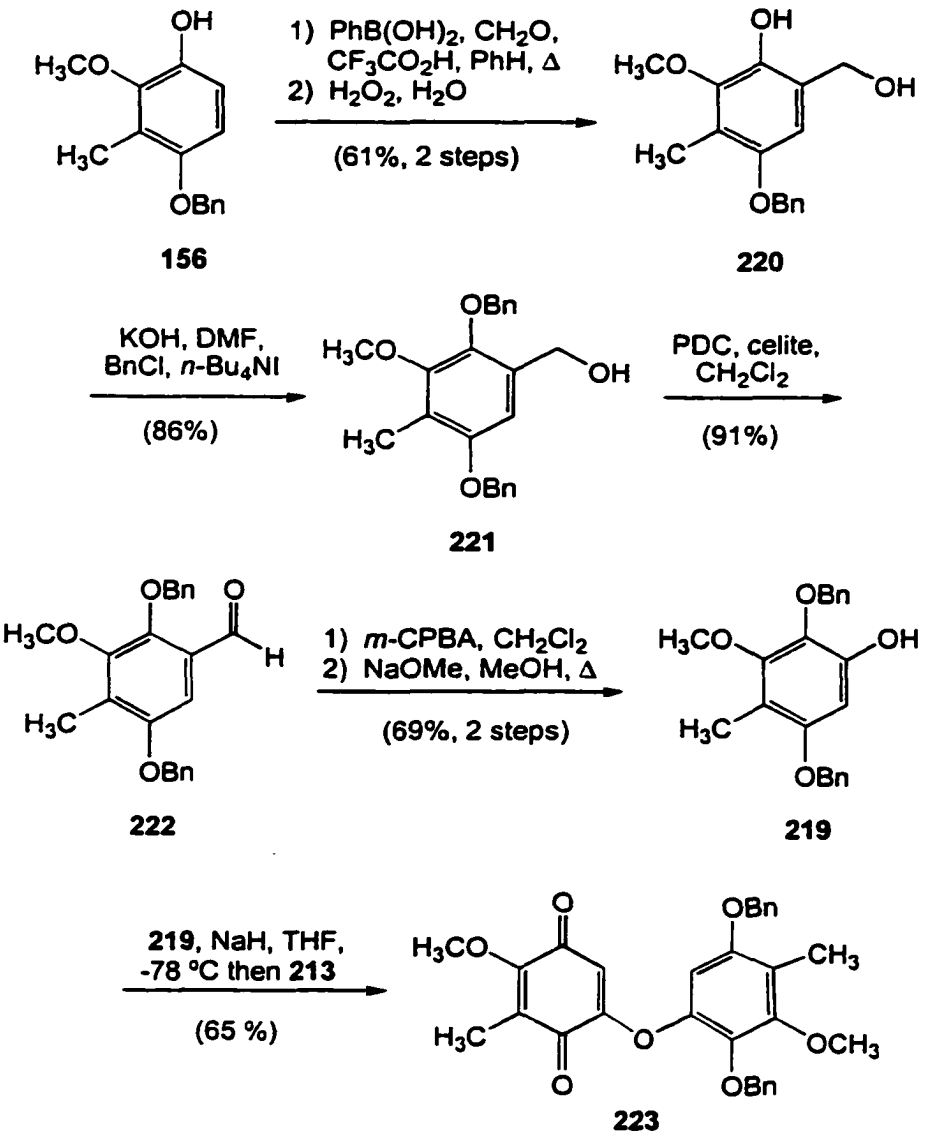
The new cyclization technique proved useful for several systems and was investigated for the synthesis of the aromatic core of popolohuanone E **216**. This required a substrate whereby the 1,4-benzoquinone portion of the aromatic core of **217** could be revealed after the cyclization. Retrosynthetically, cleavage of the central furan ring in **217** would give biaryl **218** that could be prepared from the unsymmetrical

aromatics **213** and **219** (Scheme XLVI). It was anticipated that the addition of the phenoxide ion of **219** to the chloroquinone **213** would provide the cyclization precursor **218**.



Scheme XLVI

Incorporation of a hydroxyl group into the ring system of **156** was performed by the boronic acid assisted addition to formaldehyde to provide hydroxymethyl **220** (Scheme XLVII).[92] Selective protection of the C-1 phenol as the benzyl ether formed

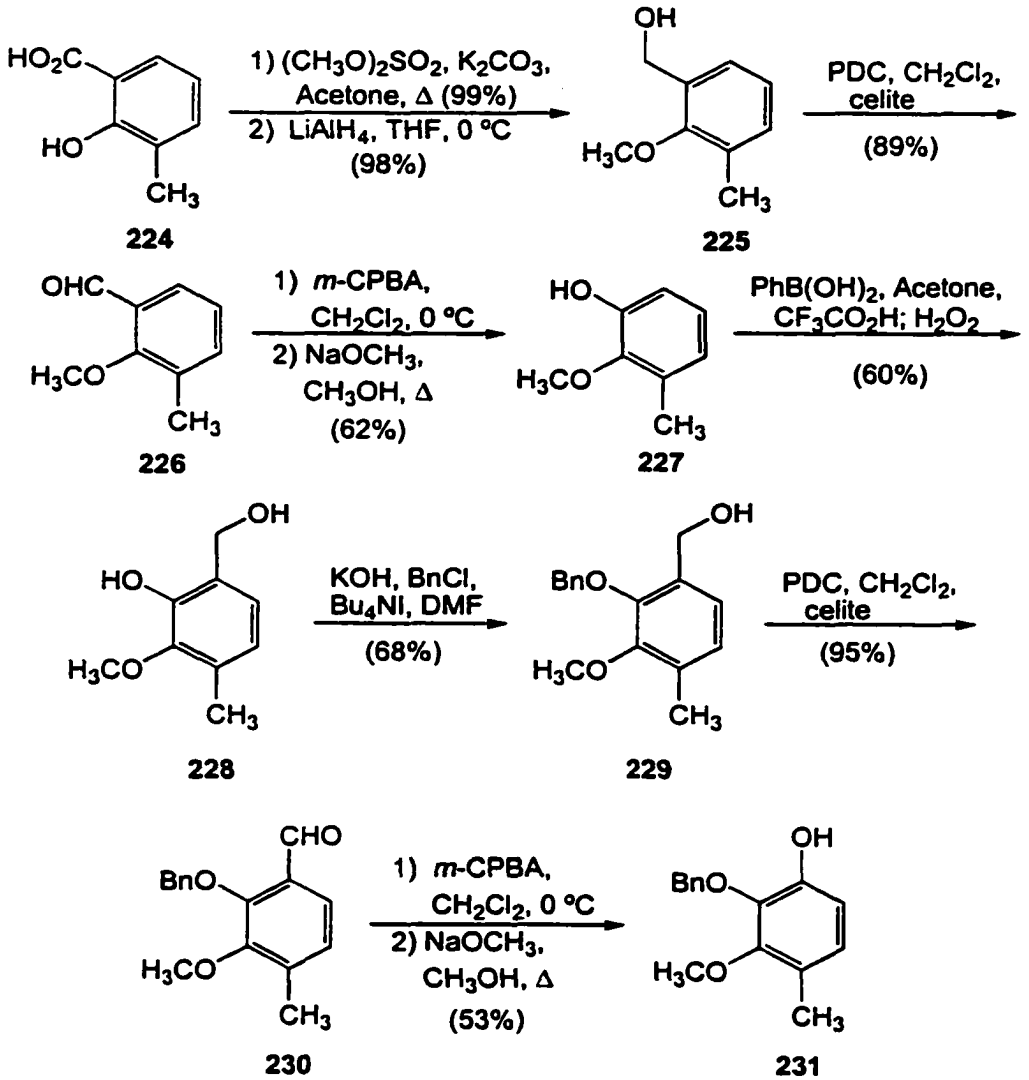


Scheme XLVII

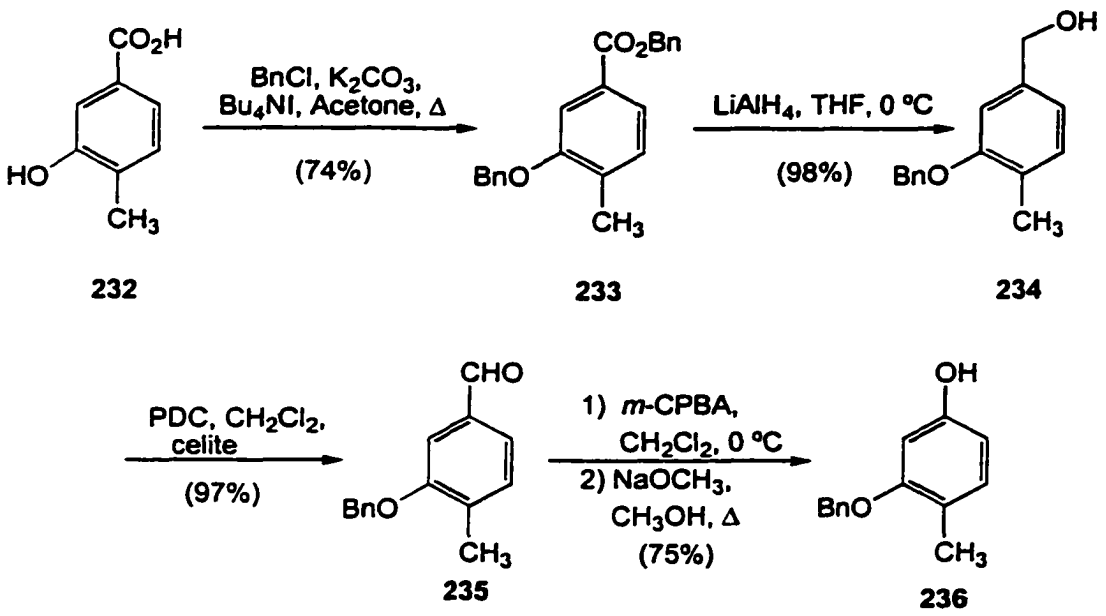
221 and oxidation of the primary alcohol gave aldehyde 222. A two-step sequence of Baeyer-Villager oxidation/saponification afforded phenol 219, however phenoxide addition to chloroquinone 213 provided the biaryl ether 223 and none of the desired C-alkylated material. This was unexpected since Terashima's method involved the addition of a phenol to a dichloroquinone using the same conditions and only resulted in the

product of C-alkylation (see Chapter 1, Scheme VI). For our case, the predominance of *O*-alkylation was most likely due to steric hindrance around the phenolic position.

The use of other appropriately substituted phenols with less congestion on the ring system was investigated. These phenols were prepared utilizing previously discussed procedures and are outlined in Schemes XLVIII and XLIX.



Scheme XLVIII



Scheme XLIX

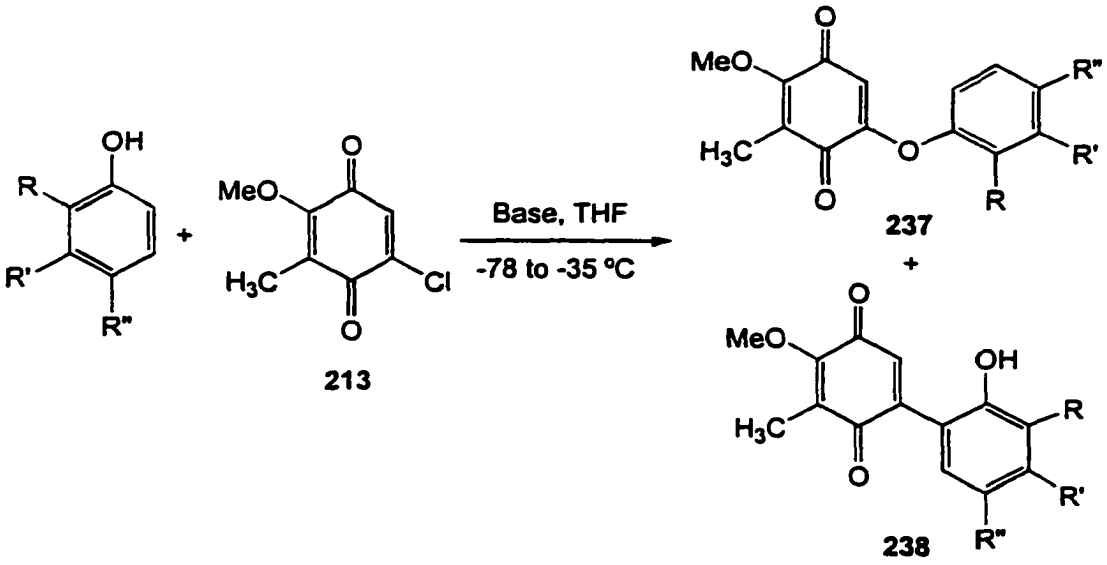
The results from the additions of these phenols to the chloroquinone **213** are outlined in Table 10. Each phenol was subjected to treatment with NaH at –78 °C and then slowly warmed to –35 °C prior to quenching the reaction with saturated ammonium chloride. From the ^{1}H NMR, the splitting pattern for the aromatic protons in the aromatic region easily allowed for the assignment of products as either O-alkylated or C-alkylated. If the product was that of O-alkylation, the AB spin system of the two aromatic protons was unaffected, however the C-alkylation product showed a single resonance in the aromatic region.

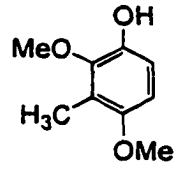
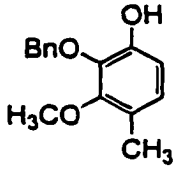
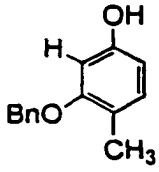
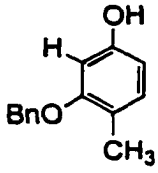
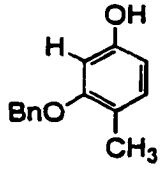
In the case of the addition of phenol **138** to the chloroquinone, the product ratio was in favor of O-alkylation. This was surprising since Terashima's studies with the identical phenol to the dichloroquinone gave only a single product (see Scheme XXXVII). Our attempts to generate Terashima's dichloroquinone were unsuccessful.

The phenoxides from **231** and **236** also gave a mixture of products from O- and

C- alkylation (runs b and c, Table 10) from addition to chloroquinone **213**. In an effort to obtain a higher percentage of C-alkylated products, bases other than NaH were investigated. Based on the hard-soft-acid-base concept,[93] the better the matched donor and acceptor pair, the better the complexation.[94] In the case of the chloroquinone **213**, the chloride ion is hard and would match best with a hard nucleophile such as a carbon ion to provide C-alkylated products, but the phenoxide ion must be tightly bound by a counterion, such as lithium, to prevent it's interference. To test this theory, potassium hydride, which contains a soft cation, and methyl lithium were assayed utilizing phenol **236** (runs d and e). For these substrates, we found that with potassium hydride, mostly O-alkylated products were obtained, which was expected, since the oxygen was not tightly bound by the cation. C-alkylation became the major product when lithium was the counter ion, however, The isolated yields were not high enough to make this a practical synthetic.

Table 10



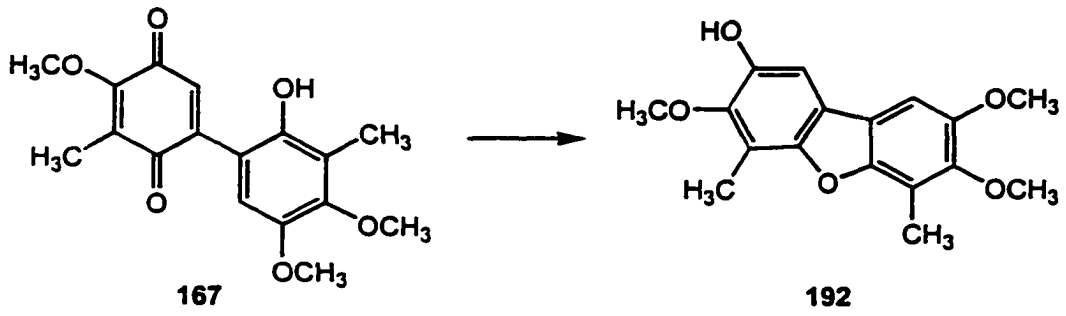
Run	Phenol		Base	237 (%) C-alkylation	238 (%) O-alkylation
a		**138**	NaH	24	32
b		**231**	NaH	22	68
c		**236**	NaH	25	52
d		**236**	CH_3Li	45	32
e		**236**	KH	30	49

We have demonstrated a mechanistic understanding of the unusual dimeric products obtained from the mild acid catalysis of hydroxy quinone **167**. The product distribution could be altered by including either oxidizing and reducing agents to obtain products derived from 1,2-intramolecular or 1,4-intermolecular cyclizations. This reductive cyclization method also was utilized to generate simple dihydrobenzofuran and dibenzofuran (e.g., 215) systems. The addition of less substituted phenols to chloroquinones does provide a general method of forming dibenzofurans, however this methodology was not applicable to the core of popolohuanone E.

Experimental Section

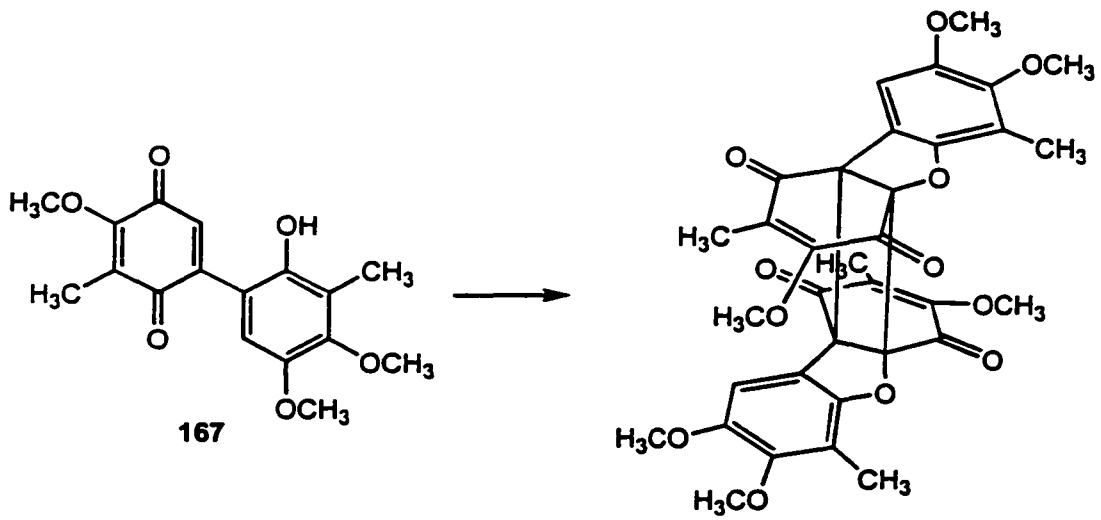
General

All reactions were run in flame-dried glassware under a nitrogen atmosphere unless otherwise noted. Diethyl ether (Et_2O) and tetrahydrofuran (THF) were distilled from sodium/benzophenone ketyl prior to use. Benzene (PhH), toluene ($PhCH_3$), and methylene chloride (CH_2Cl_2) were distilled from calcium hydride. The pyridinium *p*-toluenesulfonate was recrystallized from EtOH. All other chemicals were purchased from Aldrich Chemical Co. and were used as received. Reaction progress was monitored by TLC using E. Merck silica gel 60 F-254, and preparative TLC was performed with these plates (10 x 10 x 0.25 cm). Solvents were removed on a Buchi rotary evaporator at reduced pressure (15-20 torr).



167 192

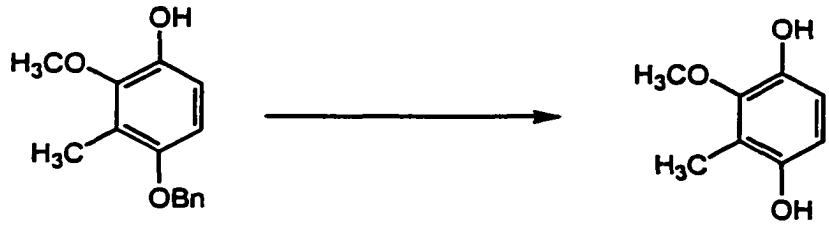
4,6-Dimethyl-2-hydroxy-3,7,8-trimethoxydibenzofuran (192). A solution of 20.0 mg (0.0630 mmol) of **167**, 6.9 mg (0.063 mmol) of 1,4-dihydroquinone, and 1.0 mg (0.00400 mmol) of PPTS in benzene (1.0 mL) was maintained at a gentle reflux in air for 2 h. The solvent was remove *in vacuo*, and the residue was purified by SiO_2 chromatography (10% EtOAc/Hexanes) to provide 12.3 mg (65%) of **192** as an off-white solid: mp 152-153 °C; R_f = 0.22 (30% EtOAc/Hexanes); IR (thin film) υ 3463, 2943, 1098, 1084, 754, 665 cm^{-1}; ^1H NMR δ 7.23 (s, 1H), 7.14 (s, 1H), 5.59 (s, 1H, exchanges with D_2O), 3.96 (s, 3H), 3.88 (s, 3H), 3.87 (s, 3H), 2.54 (s, 3H), 2.50 (s, 3H) ppm; ^{13}C NMR δ 150.3, 149.8, 149.5, 146.8, 145.0, 144.3, 120.1, 118.8, 116.1, 114.8, 102.1, 99.8, 61.4, 60.8, 56.2, 9.55, 9.20 ppm. Anal. Calcd for $C_{17}H_{18}O_5$: C, 67.54; H, 6.00;. Found: C, 67.67; H, 5.79.



167

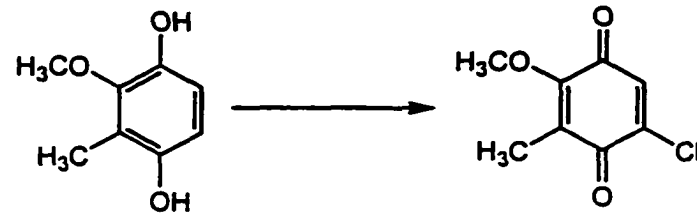
193

3,3',8,8',9,9'-Hexamethoxy-2,2',7,7'-tetramethyl-5,5',12,12'-bidibenzofurano-1,1',4,4'-quinone (193). A solution of 20.0 mg (0.063 mmol) of **167**, 146 mg (0.628 mmol) of silver oxide and 1.0 mg (0.004 mmol) of PPTS in benzene (1.0 mL) was maintained at a gentle reflux in air for 1 h. The solvent was remove *in vacuo*, and the residue was purified by SiO_2 chromatography (10% EtOAc/Hexanes) to provide 13.0 mg (66%) of **193** as an orange-brown oil; R_f = 0.13 (30% EtOAc/Hexanes); IR (thin film) υ 3013, 2942, 1675, 1641, 1610, 1487, 1282, 1097 cm^{-1}; ^1H NMR δ 6.26 (s, 1H), 4.00 (s, 3H), 3.67 (s, 3H), 3.64 (s, 3H), 1.97 (s, 3H), 1.87 (s, 3H) ppm; ^{13}C NMR δ 186.5, 177.6, 154.4, 150.0, 148.9, 148.6, 143.9, 129.5, 122.7, 119.2, 116.2, 111.6, 60.9, 60.1, 56.0, 9.9, 9.3 ppm. HRMS m/e calcd for $C_{34}H_{36}O_{12}$ (2M + $4H^+$) 636.2207, found 636.2198.



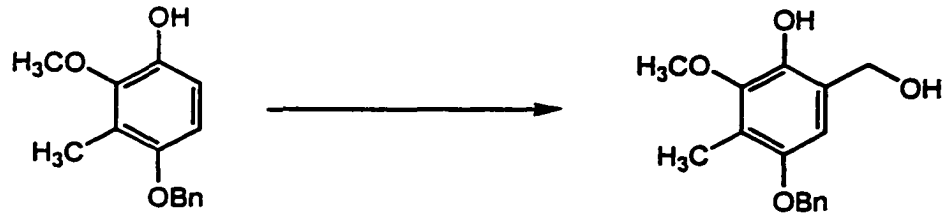
156 **212**

2-methoxy-3-methyl-1,4-dihydroquinone (212). To a solution of 0.250 g (1.02 mmol) of phenol **156** in EtOH (5.0 mL) was added 25 mg of 10% Pd on activated charcoal. The mixture was stirred under an atmosphere of H_2 for 12 h and the catalyst was removed by filtration through a pad of Celite® on a fritted funnel and the solids were washed thoroughly with CH_2Cl_2. The organics were concentrated by rotary evaporation to provide a white solid that was purified further by flash chromatography (25 g SiO_2; 50% EtOAc/Hexanes) to provide 144 mg (91%) of the phenol as a white solid: R_f = 0.45 in 50% Et_2O/Hexanes. Mp 107-108 °C; IR (thin film) υ 3350-3125 (v br), 1479, 1211, 1074, 1017 cm^{-1}; ^1H NMR δ 6.68 (d, 1H, J = 8.6), 6.49 (d, 1H, J = 8.6), 5.28 (bs, 1H, D_2O exchanges), 4.54 (bs, 1H, D_2O exchanges), 3.78 (s, 3H), 2.20 (s, 3H); ^{13}C NMR δ 147.6, 145.8, 142.7, 117.7, 112.3, 110.9, 60.9, 9.2.



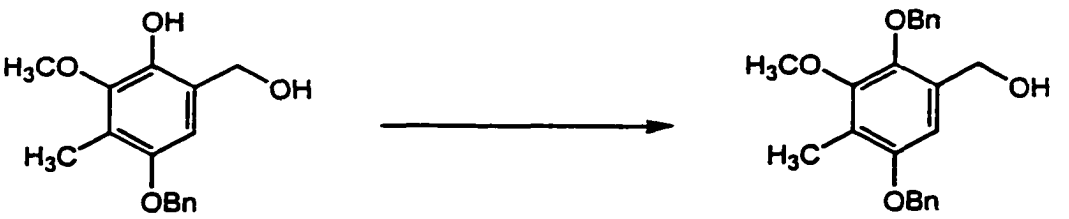
212 213

6-Chloro-2-methoxy-3-methyl-1,4-benzoquinone (213). To a solution of 100 mg (0.649 mmol) of **212** in 3.25 mL of THF was added 173 mg (1.30 mmol) of NCS. The mixture stirred for 10 minutes at room temperature. The solvent was removed *in vacuo* and the resulting yellow solid was purified further by column chromatography (25 g SiO_2; 10% EtOAc/Hexanes) to provide 73.1 mg (66%) of the chloroquinone as a yellow oil: R_f = 0.45 in 30% EtOAc/Hexanes; ^{1}H NMR δ 6.83 (s, 1H), 4.07 (s, 3H), 2.03 (s, 3H) ppm; ^{13}C NMR 181.0, 180.1, 155.5, 143.8, 131.4, 128.4, 61.0, 9.29 ppm.



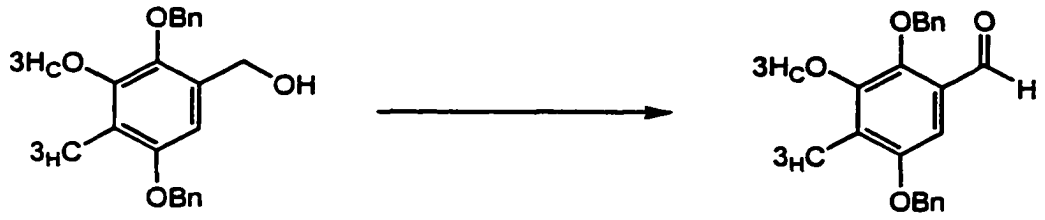
156 **220**

4-Benzyloxy-6-(α-hydroxy)methyl-2-methoxy-3-methylphenol (220). To a solution of 0.200 g (0.819 mmol) of phenol **156** in benzene (4.0 mL) was added 0.120 g (0.982 mmol) of phenylboronic acid, 0.246 g (8.19 mmol) of paraformaldehyde and 47.4 μg (0.416 mmol) of trifluoroacetic acid. The flask was fitted with a Dean Stark trap and condenser and heated at reflux for one hour. The solvent was removed *in vacuo* and the remaining solids were dissolved in THF (4.0 mL). After cooling to 0°C, 0.195 mL (1.72 mmol) of a 37% solution of H_2O_2 was added dropwise. The THF was removed *in vacuo* and the mixture was partitioned between of Et_2O and sat. Na_2CO_3 (10 mL). The organic layer was washed with brine, dried over Na_2SO_4, filtered and concentrated to a clear yellow oil. Purification by flash chromatography (20 g SiO_2; 30% EtOAc/ Hexanes) provided 136 mg (61%) of the hydroxymethylphenol as a white solid: R_f = 0.16 in 30% EtOAc/Hexanes. Mp 95-96 °C; IR (thin film) υ 3451- 3391, 2938, 1498, 1489, 1461, 1455, 1352, 1232, 1185, 1002, 736, 697 cm^{-1}; ^1H NMR δ 7.43-7.36 (m, 5H), 6.60 (s, 1H), 6.00 (bs, 1H, D_2O exchanges), 4.99 (s, 2H), 4.70 (s, 2H), 3.79 (s, 3H), 2.65 (bs, 1H, D_2O exchanges), 2.21 (s, 3H) ppm; ^{13}C NMR δ 150.5, 146.0, 141.5, 137.4, 128.5, 127.8, 127.2, 123.6, 120.1, 107.9, 70.6, 62.2, 60.9, 9.5 ppm; Anal. Calcd. for $C_{16}H_{18}O_4$: C, 70.06; H, 6.61. Found: C, 69.83; H, 6.64.



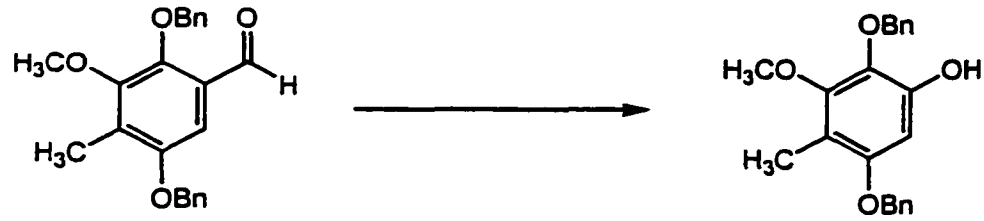
220 **221**

2,5-Dibenzyloxy-3-methoxy-4-methylbenzenemethanol (**221**). To a solution of 0.100 g (0.366 mmol) of hydroxymethylbenzene **220** in DMF (1.83 mL) was added 0.110 mL (0.329 mmol) of 3 N KOH. After stirring the mixture for 1 hour, 42 μg (0.329 mmol) of benzylchloride and 0.027 g (0.0732 mmol) of *n*-tetrabutylammonium iodide was added and the contents were stirred at room temperature for an additional 12 hours. The mixture was dissolved in Et_2O (5 mL) and washed with brine and with water (2 x 5 mL). The organic extract was dried over Na_2SO_4 , filtered, and concentrated *in vacuo*. The residue was purified by flash chromatography (10 g SiO_2; 15% EtOAc/Hexanes) to provide 85.7 mg (64%) of dibenzylated material as a white solid: R_f = 0.24 in 30% EtOAc/ Hexanes. Mp 113-114 °C; IR (thin film) υ 3417-3401, 3032, 2934, 1498, 1483, 1228, 1090, 1045, 737, 697 cm^{-1}; ^1H NMR δ 7.43 - 7.31 (m, 10H), 6.66 (s, 1H), 5.01 (s, 2H), 5.00 (s, 2H), 4.50 (s,2H), 3.85 (s, 3H), 2.22 (s, 3H), 2.00 (bs, 1H, D_2O exchanges) ppm; ^{13}C NMR δ 153.5, 151.9, 143.4, 137.4, 137.3, 131.9, 128.5, 128.4, 128.2, 127.7, 127.1, 120.9, 106.9, 75.3, 70.3, 61.3, 60.4, 9.1 ppm; Anal. Calcd. for $C_{23}H_{24}O_4$: C, 75.80; H, 6.64. Found: C, 75.76; H, 6.58.



221 **222**

2,5-Dibenzyloxy-3-methoxy-4-methylbenzaldehyde (**222**). A solution of 0.763 g (2.09 mmol) of hydroxymethylbenzene **221** in CH_2Cl_2 (10.0 mL) was stirred while 1.57 g (4.19 mmol) of PDC and 2.09 g Celite® was added. After 2 hours, the mixture was filtered through a pad of Celite® and then concentrated *in vacuo* to a yellow oil which was purified by flash chromatography (75 g SiO_2; 10% EtOAc/Hexanes) to provide 0.691 g (91%) of **222** as a light yellow solid: R_f = 0.58 in 30% EtOAc/Hexanes. Mp 77-78°C; IR (thin film) υ 3033, 2955, 2928, 2857, 1686, 1281, 1198, 1024, 737, 698 cm^{-1}; ^1H NMR δ 10.14 (s, 1H), 7.46 – 7.34 (m, 10H), 7.10 (s, 1H), 5.12 (s, 2H), 5.07 (s, 2H), 3.91 (s, 3H), 2.29 (s, 3H) ppm; ^{13}C NMR δ 189.4, 153.7, 152.3, 149.7, 136.7, 136.2, 130.1, 128.7, 128.6, 128.5, 128.4, 127.9, 127.8, 127.6, 127.2, 103.3, 76.8, 70.2, 60.7, 9.95 ppm.



222 **219**

2,5-Dibenzyloxy-3-methoxy-4-methylphenol (219). To a solution of 66 mg (0.183 mmol) of benzaldehyde **222** in CH_2Cl_2 (1.00 mL) was added 47 mg (0.272 mmol) of *m*-CPBA. The mixture was stirred 12 h and then washed with $NaHCO_3$ (3 x 3 mL), water and brine. The organic layer was dried over Na_2SO_4, filtered and concentrated to a yellow oil that was used without further purification. The crude residue was dissolved in methanol (1.0 mL) and 14 μL (0.285 mmol) of 25% wt/wt sodium methoxide was added. The solution was heated for three hours and the solvent removed *in vacuo* to provide a dark brown oil that was dissolved in EtOAc (3 mL) and washed with saturated aqueous NH_4Cl. The aqueous layer was back-extracted with additional EtOAc (2 x 3 mL) and the combined organic layers were washed with brine (5 mL). The organic extract was dried over Na_2SO_4, filtered and concentrated *in vacuo* to provide an oil that was purified by flash chromatography (10 g SiO_2; 30% EtOAc/Hexanes) provided 44 mg (69%) of the phenol as a white solid: R_f = 0.45 in 30% Et_2O/Hexanes. Mp 96-97 °C; IR (thin film) υ 3522 – 3452, 3032, 2989, 1601, 1498, 1251, 1128, 1024, 696 cm^{-1}; ^1H NMR δ 7.43 – 7.33 (m, 10H), 6.34 (s, 1H), 5.44 (s,1H), 5.00 (s, 2H), 4.97 (s, 2H), 3.87 (s, 3H), 2.14 (s, 3H) ppm; ^{13}C NMR δ 153.5, 151.5, 147.3, 137.2, 132.6, 128.7, 128.5, 127.7, 127.1, 112.0, 95.6, 75.7, 70.3, 60.5, 8.5 ppm.

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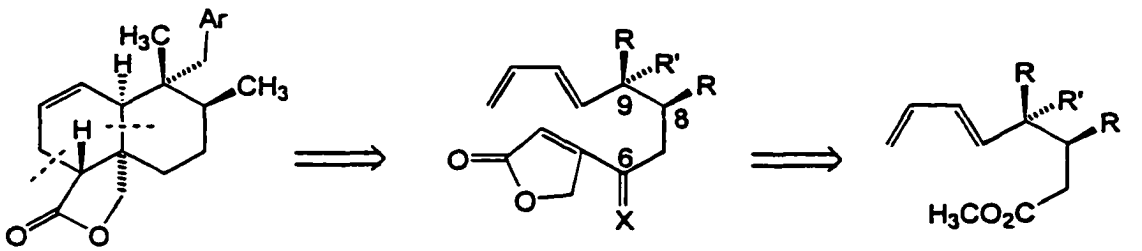
Chapter 3

Diene Precursors for Decalin Synthesis

Introduction

The use of the intramolecular Diels-Alder (IMDA) cyclization is an attractive route to construct the *cis*-decalin ring system of popolohuanone E, especially if the cyclization precursor contained the C-8 and C-9 stereocenters present in the natural product. While the results from intermolecular versions of this reaction can be predicted empirically, the results from the IMDA reaction do not follow this trend. Therefore, a study was planned that focused on the effect of different alkyl tether substituents at C-8 and C-9 or different substituents at C-6, such as a carbonyl group **240** or an alkoxyl group **241** (Figure 37). These optimized cyclization conditions would be utilized to access the *cis*-decalin systems of other natural products and of popolohuanone E. The preparation of a series of dienes **242a-e** with the requisite stereocenters was required for this study.



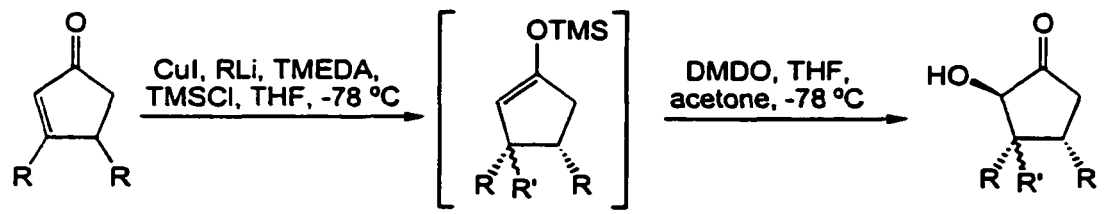
239 **240** X = O, **241** X = OR, H **242**

242	R	R'
a	H	CH_3
b	H	CH_2=CH
c	CH_3	CH_3
d	CH_3	$PhCH_2$
e	CH_3	CH_2=CH

Figure 37

Results and Discussion

The dienes were prepared from the commercially available cyclopentenone **243a** and the easily prepared cyclopentenone **243b**.[95] The conjugate addition of Gilman reagents (RMgX or RLi, CuI) to the enones was facilitated by the trapping of the enolate with trimethylsilyl chloride (TMSCl) (Scheme L).[96] Utilizing a modification of Johnson's procedure,[97] *N,N,N',N'*-tetramethylethylenediamine was added after the enone was consumed (as noted by TLC analysis) because its presence in the cuprate mixture prior to the addition destroyed the cuprate and prevented the delivery of the alkyl group to the substrate.



243a R = H
243b R = CH_3

244

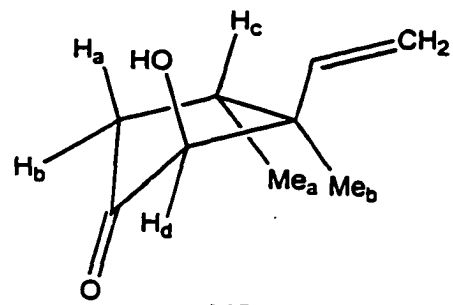
245

Entry	R	RLi	245 (%)
a	H	CH_3Li	92
b	H	$(CH_2=CH)_2Li$	90
c	CH_3	CH_3Li	79[98]
d	CH_3	$PhCH_2MgCl$	75[98]
e	CH_3	$(CH_2=CH)_2Li$	87

Scheme L

Oxidation of the intermediate silyl enol ether with dimethyldioxarane (DMDO)[99-101] resulted in the formation of α-hydroxy ketones **245a-e**. The Rubottom conditions (RCO_3H)[102,103] were utilized initially for the cleavage reaction, but they were not as chemoselective for the enol ether; the peroxyalkanoic acids gave appreciable quantities (>30%) of the ketone from competitive hydrolysis. In comparison, the DMDO oxidation was fast, it did not require a separate step to cleave the silyl ether and it was completely selective for the silyl enol ether; no comptetitive or over-oxidation of mono-substituted olefins was observed (entries b and e).

The diastereoselectivity of the addition could be determined from the ratio of the two vinylic enol ether resonances present in the ^1H NMR spectra of the crude reaction mixtures ($\delta \approx 4.10$-4.80 ppm). For the case of the divinyl cuprate addition to 2,3-dimethylcyclopentenone (entry e), careful repetitive column chromatography provided the major diastereomer of the α-hydroxy ketone mixture. An NOE difference study allowed the assignment of the relative configuration of the two methyl groups.[104]



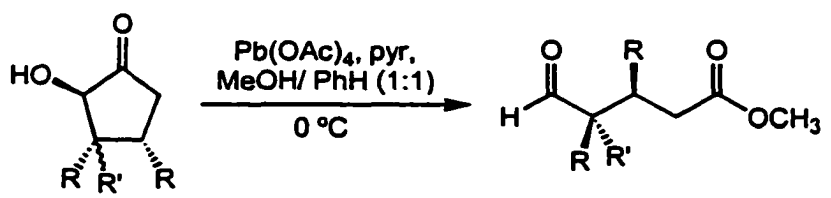
245e

Observed NOE (%)
Irradiate Me_a - H_b (2)
- H_d (2)
- H_c (10)
Irradiate Me_b - H_d (4)

Figure 38

Irradiation of the methyl group at δ 1.13 (Me_a) produced enhancements of the resonance at δ 2.39 (H_c), the signal at δ 3.96 (H_d) and that at δ 2.06 (H_b). This latter resonance was assigned to the proton in the plane with the methylene α- to the carbonyl (Figure 38). The irradiation of the methyl resonance at δ 1.22 (Me_b) also gave enhancements of the signal at δ 3.96 (H_d) thereby providing an unambiguous assignment of the structure. We were pleased that the addition occurred in the desired mode, *anti-* to the γ-methyl substituents.

The oxidative cleavage of the α-hydroxy ketones **245a-e** to form the aldehydic esters **246a-e** was accomplished with methanolic $Pb(OAc)_4$[105] (Scheme LI). Highly substituted cases (entries c-e) required the addition of a pyridine buffer because

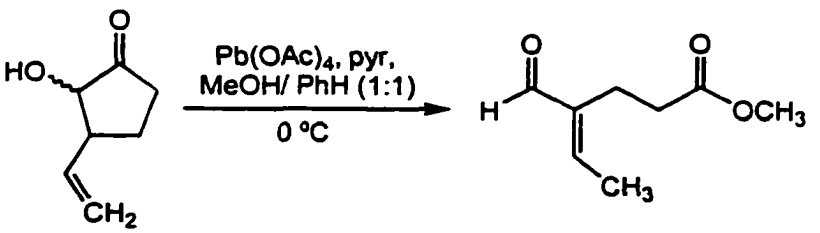


245 **246**

Entry	R	R'	**246** (%)
a	H	CH_3	74
b	H	CH_2=CH	-
c	CH_3	CH_3	90[98]
d	CH_3	$PhCH_2$	92[98]
e	CH_3	CH_2=CH	98

Scheme LI

the neopentyl aldehydes were extremely sensitive and underwent rapid auto-oxidation to the acid. For entry b, the product from the cleavage of α-hydroxy ketone **246b** rapidly isomerized to the conjugated enal **247** in the presence of pyridine (Scheme LII); therefore, the buffer was eliminated from the reaction and the crude product was utilized without further purification. Even during characterization, the isomerization to the enal still occurred upon exposure to silica gel.

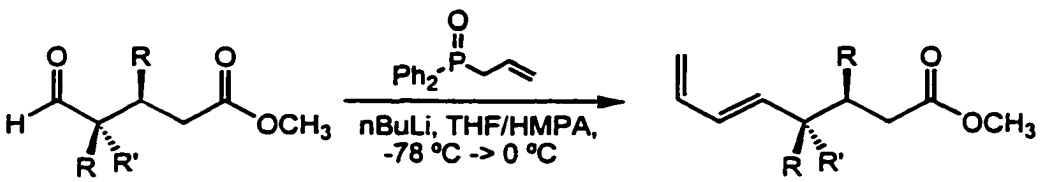


246b **247**

Scheme LII

Several methods to homologate the aldehydes to the desired E-dienes were surveyed.[106] Use of the allyl Wittig reagent provided a moderate yield of the diene as a mixture of *Z/E* isomers that would have to be isomerized to the *E* isomer to be useful for the IMDA. The Julia-Lythgoe sulfone protocol[107] was also investigated, but the reductive elimination of the diastereometric β-acetoxysulfones provided mainly vinyl sulfone products. The sequential Wittig homologation process utilizing a stabilized ylide, followed by reduction, oxidation and Wittig methylene, was not only tedious and lengthy, but the reaction of the stabilized ylide with the neopentyl substrates required vigorous reaction conditions and led to extensive decomposition of the starting material.

Yamamoto's allyl diphenylphosphine reagent,[108] a highly nucleophilic reagent that was easily handled, provided the diene in a single transformation with excellent stereocontrol (>95/5 *E*/*Z*) (Scheme LIII).



246 **248**

Entry	R	R'	248 (%)
a	H	CH_3	87
b	H	CH_2=CH	63
c	CH_3	CH_3	74[98]
d	CH_3	$PhCH_2$	77[98]
e	CH_3	CH_2=CH	70[106]

Scheme LIII

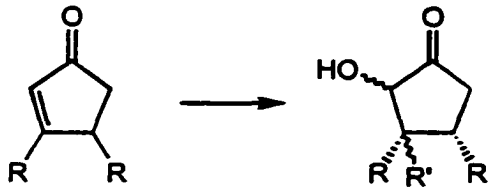
The sequence above outlines a general and stereoselective synthesis of substituted dienes. The *syn*-methyl orientation can be incorporated with a high degree of stereoselectivity and this methodology is well suited to access the highly functionalized decalin ring systems of the clerodanes and other decalin containing natural products. Transformation of the ester moiety into an aldehyde, iodide or a Weinreb amide would allow the diene portion to be coupled with a dienophile prior to an IMDA cyclization.

Experimental Section

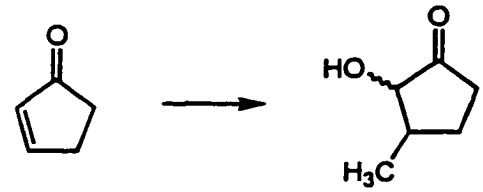
General Procedure

All reactions were performed in flame-dried glassware and kept under a nitrogen atmosphere. Diethyl ether (Et_2O) and tetrahydrofuran (THF) were distilled from sodium/benzophenone ketyl prior to use. Benzene (PhH), toluene ($PhCH_3$), tetramethyl-ethylenediamine (TMEDA), Hexamethyl-phosphoramide (HMPA) trimethylsilyl chloride (TMSCl) and methylene chloride (CH_2Cl_2) were distilled from calcium hydride prior to use. Dimethylsulfoxide (DMS) was distilled from sodium metal prior to use. The cuprous iodide (CuI) was purified following the procedure of Whitesides.[109] Dimethyldioxirane (DMDO) solutions were prepared following Murrays's procedure[101] and stored in the freezer for up to one week. The 3,4-dimethylcyclopentenone was synthesized from crotonic acid following Conia's procedure.[95] All other chemicals were purchased from Aldrich chemical company and were used as received. Reaction progress was monitored by TLC using E. Merck silica gel 60 F-254. Solvents were removed on a Buchi rotary evaporator at reduced pressure (15-20 torr).

For the α-hydroxy ketones, the ^1H and ^{13}C NMR data are given for the major diasteromer since they were obtained as a mixture of diastereomers and were not separated unless otherwise noted. Several of the aldehydes derived from the lead tetraacetate ($Pb(OAc)_4$) cleavage were prone to auto-oxidation; therefore, only the ^1H NMR and IR spectra were recorded for these compounds.

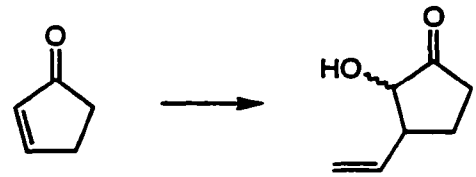


General Procedure for the Formation of α-Hydroxyketones: To a suspension of CuI (1.1 mmol) in dry THF (4.0 mL) at -78 °C was added the appropriate organometallic reagent (1.1 mmol for alkyl cuprates, RCuI, and 2.2 mmol for dialkyl cuprates, R_2CuI). The mixture was stirred for 20 minutes to allow for formation of the copper reagent. To this was added trimethylsilylchloride (TMSCl) (2.4 mmol) followed by the enone substrate (1.0 mmol) in THF (1.5 mL). After consumption of the enone (by TLC analysis), TMEDA (2.4 mmol) was added and the mixture was warmed to 0 °C during 15 min. After dilution with pentane (8.0 mL), the resulting precipitate was removed by filtration through a pad of Celite and thoroughly washed with additional pentane. The filtrate was transferred to a separatory funnel and washed with cold 0.1 N HCl solution (50 mL), 0.1 N $NaHCO_3$ solution (50 mL) and brine (2 x 50 mL). The organic layer was dried over Na_2SO_4, filtered and concentrated to provide the crude silyl enol ether as a clear yellow oil. The oil was redissolved in THF (15 mL) and cooled to -78 °C prior to the addition of freshly prepared solution of DMDO in acetone (1.1 mmol). After 5-10 min the oxidation was complete (TLC analysis) and the solvents were removed by rotary evaporation to provide a residue that was purified by flash chromatography on SiO_2 (20% EtOAc/Hexanes) to provide the α-hydroxyketone as either a solid or an oil.



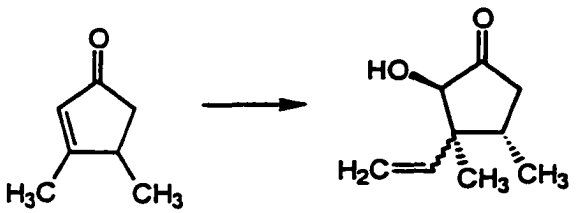
243a **245a**

(2R*, 3R*)-2-Hydroxy-3-methylcyclopentanone (245a). Colorless oil; R_f = 0.16 in 30% EtOAc/Hexanes; IR (neat) v 3430 (br), 2959, 2932, 1751, 1461, 1127, 1107, 1061, 1028, 670, 665 cm^{-1}; ^1H NMR (1:1 mixture of diastereomers) δ 4.20 (br d, J = 5.8 Hz, 0.5H), 3.62 (d, J = 11.5 Hz, 0.5H), 2.92 (d, J = 2.6 Hz, 0.5H, exchanges with D_2O), 2.80 (d, J = 2.9 Hz, 0.5H, exchanges with D_2O), 2.67-2.53 (m, 0.5H), 2.49-2.00 (m, 3H), 1.98-1.54 (m, 1H), 1.51-1.40 (m, 0.5H), 1.26 (d, J = 6.4 Hz, 1.5H), 0.87 (d, J = 7.2 Hz, 1.5H0 ppm; ^{13}C NMR (major diasteromer) δ 218.3, 82.0, 38.5, 34.0, 24.9, 18.0 ppm; (minor diastereomer) δ 218.3, 78.7, 33.7, 30.7, 23.4, 12.3 ppm.



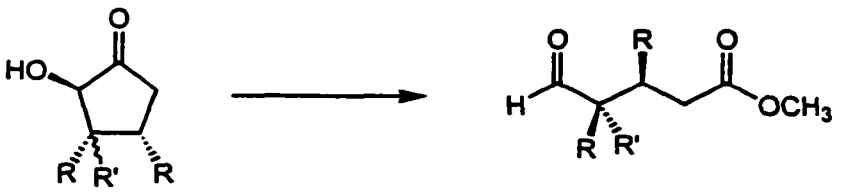
243a **245b**

(2R*, 3R*)-2Hydroxy-3-vinylcyclopentanone (**245b**). Colorless oil; R_f = 0.28 in 30% EtOAc/Hexanes; IR (neat) v 3420 (br), 2958, 2940, 2877, 1748, 1641, 1404, 1109, 1040, 1055, 1016, 995, 917, 670, 665 cm^{-1}; ^1H NMR (major diastereomer) δ 5.87 (ddd, *J* = 17.3, 10.0, 7.0 Hz, 1H), 5.21 (d, *J* = 17.3 Hz, 1H), 5.13n (d, *J* = 10.0 Hz, 1H), 3.80 (dt, *J* = 11.5, 2.1, Hz, 1H), 2.72 (d, *J* = 2.7 Hz, 1H, exchanges with D_2O), 2.52-2.37 (m, 2H), 2.24-2.05 (m, 2H), 1.71-1.61 (m, 1H) ppm; ^{13}C NMR (major diastereomer) δ 216.6, 138.2, 116.5, 80.0, 47.6, 33.4, 22.8 ppm; (minor diastereomer) δ 216.6, 134.0, 117.7, 78.1, 43.4, 31.4, 21.9 ppm.



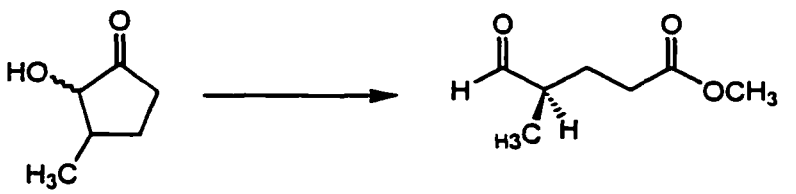
243b **245e**

(2R*, 3S*, 4S*)-3,4-Dimethyl-2-hydroxy-3-vinylcyclopentanone (245e). Colorless oil; R_f = 0.29 in 25% EtOAc/Hexanes; IR (thin film) v 3444 (br), 3124, 3045, 2964, 2032, 2876, 1752, 1451, 1406, 1380, 1158, 1081, 1006, 916 cm^{-1}; ^1H NMR (major diastereomer) δ 5.75 (dd, J = 17.7, 11.1 Hz, 1H), 5.06 (br d, J = 11.1 Hz, 1H0, 5.03 (br d, J = 17.8 Hz, 1H0, 3.84 (d, J = 1.4 Hz, 1H), 3.07 (br s, 1H, exchanges with D_2O), 2.49 (dd, J = 19.4, 9.1 Hz, 1H), 2.35-2.25 (m, 1H), 1.96 (ddd, J = 19.4, 4.5, 1.8 Hz, 1H), 1.09 (s, 3H), 1.01 (d, J = 7.8 Hz, 3H) ppm; ^{13}C (major diastereomer) 216.92, 139.97, 114.81, 80.86, 46.93, 40.86, 33.4, 18.45, 16.62 ppm; (minor diastereomer) 217.51, 141.44, 114.16, 78.43, 40.38, 35.57, 18.92, 18045 ppm.



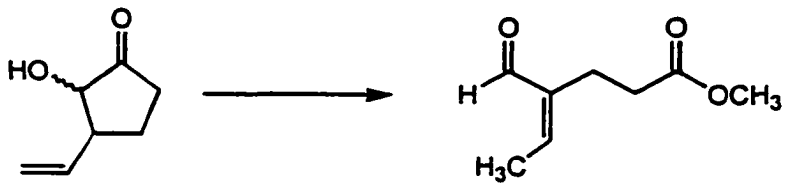
General Procedure for Aldehydic Ester Formation:

To a solution of α-hydroxyketone (1.0 mmol) and pyridine (2.2 mmol) in a 1:1 mixture of PhH/CH_3OH (6.0 mL) at 0 °C was added $Pb(OAc)_4$ (1.1 mmol). The mixture stirred for 2 h and then diluted with Et_2O (30 mL). The mixture was transferred to a seperatory funnel and washed with 50% $CuSO_4$ solution (30 mL) and brine (2 x 30 mL). The organic layer was removed and dried over Na_2SO_4, filtered and concentrated to provide the crude product as an oil that were purified by SiO_2 chromatography (10 % EtOAc/Hexanes) to provide the aldehydic esters as oils.



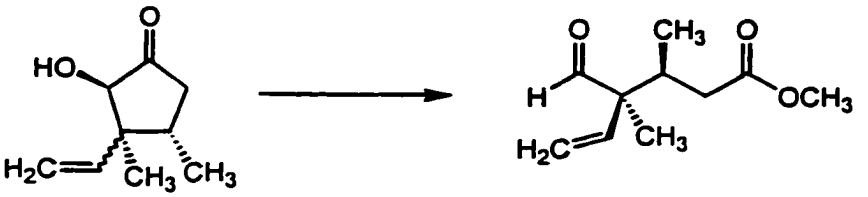
245a **246a**

Methyl 4-Methylpentan-5-aloate (246a). Colorless oil; R_f = 0.46 in 30% EtOAc/Hexanes; IR (neat) v 2956, 2938, 2817, 2719, 1737, 1459, 1438, 1259, 1196, 1175, 671, 665 cm^{-1}; ^1H NMR δ 9.63 (d, J = 1.7 Hz, 1H), 3.68 (s, 3H), 2.48-2.37 (m, 1H), 2.38 (t, J = 7.60 Hz, 1H), 2.17-2.00 (m, 1H), 1.76-1.63 (m, 1H), 1.13 (d, J = 7.1 Hz, 3H) ppm.



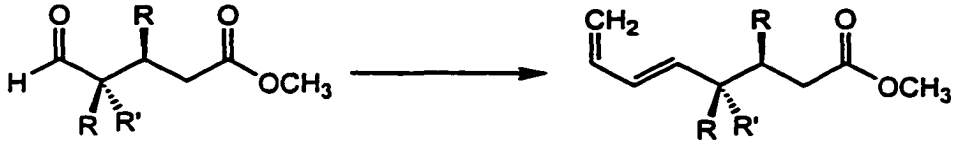
245b 247

Methyl 4-formyl-4*Z*-hexenoate (247). Colorless oil; R_f = 0.45 in 30% EtOAc/Hexanes; IR (neat) v 2953, 2847, 2718, 1738, 1685, 1254, 1199, 1018, 989, 671 cm^{-1}; ^1H NMR δ 9.37 (s, 1H), 6.66 (q, *J* = 7.0 Hz, 1H), 3.66 (s, 3H), 2.59 (t, *J* = 7.5 Hz, 2H), 2.43 (t, *J* = 7.5 Hz, 2H), 2.03 (d, *J* = 7.0 Hz, 3H) ppm; ^{13}C NMR δ 194.7, 173.3, 151.2, 142.6, 51.6, 32.2, 19.3, 14.8 ppm.

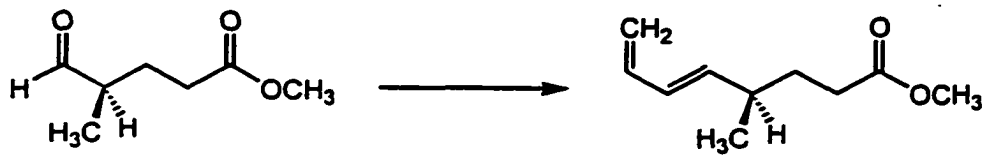


245e 246e

Methyl (3S*, 4S*)-4-Carboxal-3,4-dimethylhex-5-enoate (246e). Colorless oil; R_f = 0.53 in 30% EtOAc/Hexanes; IR (neat) v 2978, 2843, 2709, 1737, 1633, 1458, 1259, 1054, 671 cm^{-1}; ^1H NMR (major diastereomer) δ 9.41 (s, 1H), 5.81 (dd, J = 17.6, 10.8 Hz, 1H), 5.36 (d, J = 10.8 Hz, 1H), 5.16 (d, J = 17.6 Hz, 1H), 3.68 (s, 3H), 2.33 (dd, J = 18.0, 3.6 Hz, 1H), 2.07 (dd, J = 18.0, 10.4 Hz, 1H), 1.11 (s, 3H), 0.93 (d, J = 6.8 Hz, 3H) ppm; ^1H NMR (minor diastereomer) δ 9.39 (s, 1H), 5.78 (dd, J = 17.6, 10.4 Hz, 1H), 5.36 (d, J = 10.8 Hz, 1H), 5.20 (d, J = 17.6 Hz, 1H), 3.68 (s, 3H), 2.50-2.58 (m, 2H), 2.46 (br d, J = 18.0 Hz, 1H), 1.99 (dd, J = 10.8, 18.0 Hz, 1H), 1.10 (s, 3H), 0.90 (d, J = 6.8 Hz, 3H) ppm.

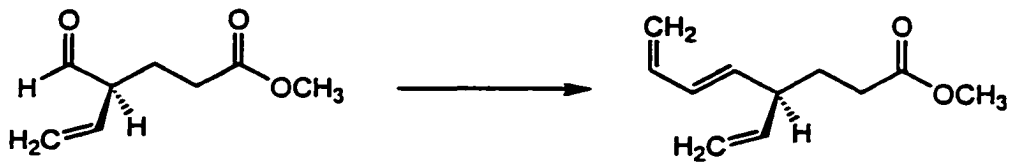


General Procedure for the Formation of the Dienes: To a solution of the allyl phosphine oxide[103] (1.6 mmol) in a 20:1 mixture of THF/HMPA (6.5 mL) at –78 °C was added *n*-BuLi (1.5 mmol). The mixture stirred for 30 min to insure generation of the anion. To the anion was added a solution of the aldehydic ester **246a** (1.0 mmol) in THF (2.5 mL). After stirring 1 h at –78 °C, the mixture was warmed to 0 °C for 1 h and then warmed to room temperature. Sat. NH_4Cl solution (5.0 mL) was added to the mixture followed by Et_2O (5.0 mL). The organic layer was separated and washed with 50% $CuSO_4$ (20 mL) and brine (2 x 20 mL). The organic layer was dried over Na_2SO_4, filtered and concentrated to an oil that was purified by SiO_2 chromatography to provided the diene as a mixture of olefin isomers that could be equilibrated to >99% *E* by dissolution in PhH and treatment with a catalytic amount of I_2.



246a 248a

Methyl 4-methylocta-5*E*-7-dienoate (248a). Colorless oil; R_f = 0.61 in 30% EtOAc/Hexanes; IR (neat) v 2956, 2928, 2870, 1740, 1651, 1456, 1436, 1261, 1192, 1175, 1005, 899 cm^{-1}; ^1H NMR δ 6.20 (dt, *J* = 16.9, 10.1 Hz, 1H), 5.95 (dd, *J* = 15.1, 10.1 Hz, 1H), 5.45 (dd, *J* = 15.1, 8.3 Hz, 1H), 5.03 (d, *J* = 16.9, 1H), 4.90 (dd, *J* = 10.1, 0.70 Hz, 1H), 3.58 (s, 3H), 3.58 (s, 3H), 2.29-2.05 (m, 3H), 1.63-1.52 (m, 2H), 0.95 (d, *J* = 6.8 Hz, 3H) ppm; ^{13}C δ 174.2, 139.6, 137.0, 130.1, 115.4, 51.5, 36.5, 32.0, 31.7, 20.4 ppm.



246b 248b

Methyl 4-vinylocta-5*E*-7-dienoate (**248b**). Colorless oil; R_f = 0.73 in 30% EtOAc/Hexanes; IR (neat) v 2996, 2975, 2952, 2931, 1739, 1437, 1253, 1193, 1175, 1105, 915, 672 cm^{-1}; ^1H NMR δ 6.29 (dt, *J* = 17.0, 10.3 Hz, 1H), 6.04 (dd, *J* = 15.3, 10.5 Hz, 1H), 5.68-5.57 (m, 1H), 5.54 (dd, *J* = 15.3, 7.7 Hz, 1H), 5.11 (d, *J* = 16.8 Hz, 1H), 5.04-4.98 (m, 3H), 3.60 (s, 3H), 2.67 (pentet, *J* = 7.4 Hz, 1H), 2.25 (t, *J* = 7.5 Hz, 1H), 1.69 (q, *J* = 7.6 Hz, 1H) ppm; ^{13}C NMR δ 173.7, 140.0, 136.9, 136.0, 131.4, 116.0, 115.1, 51.5, 46.1, 31.8, 29.4 ppm.

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Curriculum Vitae
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Professional Objective

To obtain a position teaching organic chemistry and other advanced courses to college students and to conduct research involved with the novel synthesis of compounds for the treatment of contemporary diseases.

Education

Ph.D. in Chemistry (major: Organic)
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Lehigh University, Bethlehem, PA 18015.

B.S. in Chemistry
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Teaching Experience

Organic Chemistry Lab, Chemistry Department, Lehigh University, Fall 1991, 1992, and 1995. Presented the pre-lab lectures, ordered and maintained laboratory supplies, supervised undergraduates.

Chem 52. Organic Chemistry I, Chemistry Department, Lehigh University Fall 1991, 1992, and 1995. Devised homework assignments, graded and proctored exams, contributed to exam questions, presented recitations, voluntarily held pre-exam tutorials.

Chem 353. Organic Analysis Lab, Chemistry Department, Lehigh University, Spring 1992 and 1993. Supervised undergraduates in the laboratory, operated instrumentation, performed the pre-lab preparation of solutions, presented several lectures throughout the semester.

General Chemistry Laboratory, Chemistry Department, Lehigh University, Spring 1994 and 1995. Laboratory preparation for 9 sections, including solvents, solutions and instrumentation.

Spectroscopic Analysis, Chemistry Department, Lehigh University, Fall 1993 and 1994. Graded graduate level course assignments and exams for on-campus students and 50 off-campus students (satellite program).

Work Experience

Researcher/Supervisor, Orasure Technologies, Bethlehem, PA, 1998– present. Directed several post-docs in the synthesis division, devised synthetic projects, prepared haptens and immunogens to be developed into immunoassays.

Research Assistant for John W. Benbow, Chemistry Department, Lehigh University, 1994-present. Researched the synthesis of natural products, perfected skills on microscale quantities, assisted in writing several research papers, responsible for ordering supplies for the research labs while under a strict budget, supervised several undergraduate research projects, in charge of waste disposal.

Research Assistant for Ned D. Heindel, Chemistry Department, Lehigh University, 1991-1993. Prepared analogs of dextran for potential pharmaceutical use as scaffolds for transport and/or the controlled release of drugs.

Undergraduate Researcher for Hans-Georg Gilde, Marietta College, 1988-1990. Conducted research involving the use of Lanthanide shift reagents for simplifying complex ^{1}H NMR spectra.

Undergraduate Laboratory Assistant for William Hohman, Marietta College, 1988-1990. Prepared solutions required by the General Chemistry Laboratory courses.

Laboratory Technician, GE Plastics, Washington, WV, Summer 1989. Synthesized and analyzed the durability of new weather- and impact-resistant plastics for automobile moldings.

Laboratory Technician, Shell Chemical Company, Belpre, Ohio, Summer 1988. Performed quality control in their analytical laboratories.

Honors/ Awards

Lehigh University: Arts and Science Scholar, 1996-1998. First Prize at The Association for Women in Science (AWIS) poster competition, 1997.

Marietta College: Phi Beta Kappa, 1990; Departmental Honors, cum laude, Lavallee Award from the Upper Ohio Valley American Chemical Society, 1990; Alpha Lambda Delta National Honor Society, 1989; Dyer Chemistry Scholarship, 1988 and 1989; E. L. Krause Sophomore Chemistry Award, 1988; American Chemical Society Sophomore Chemistry Award, 1988;
E. B. Krause General Chemistry Award, 1987.

Professional Societies	American Chemical Society, Organic Division, 1990-present. Sigma Xi, The Scientific Research Society, 1998-present. Vice President of the Student Affiliate of the American Chemical Society, 1990.
Thesis Title	I. Model Studies on the Formation of the Dibenzofuranoquinone Core of Popolohuanone E. II. Diene Precursors for Decalin Synthesis.
Publications/ Presentations	J. W. Benbow, B. L. Martinez, R. Katoch-Rouse, "Approaches to the Benzofuranoquinone Core of Popolohuanone E," The 217th ACS National Meeting, Division of Org. Chem., Report 420, Anaheim, CA (March 21-25, **1999**).

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